- PK - SC-58635 was absorbed systemically and plasma levels of SC-58635 increased non-proportionally with dose. The mean PK parameters are presented in the following table.

PK Parameter	10 mg/kg		30 mg/kg		100 mg/kg	
	Gestation Day 6	Gestation Day 17	Gestation Day 6	Gestation Day 17	Gestation Day 6	Gestation Day 17
AUC_{0-24} (μg•hr/ml)	45.7	47.6	54.3	104	140	115
AUC/Dose	4.57	4.76	1.81	3.47	1.4	1.15
C_{max} (μg/ml)	3.79	3.20	4.91	5.43	7.66	- 7.41
C_{max}/Dose	0.379	0.320	0.164	0.181	0.0766	0.0741
T_{max} (hr)	3.00	3.00	3.00	4.00	4.00	3.00

2.4.2.3. A Range-Finding Study of SC-58635 In Pregnant Rabbits, Document No.: PSA95S-30-EX4310; Date: 27-Mar-1995 (Vol. 1.60, p. 1-69)

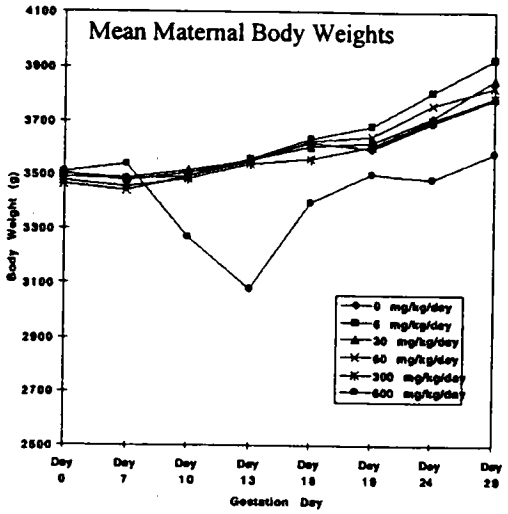
Included as an appendix to this report was:
Searle Memo Report Of SC-58635 Plasma Concentrations In A Range-Finding Study Of SC-58635 In Pregnant Rabbits, EX4310, Document No.: MRC-95S-0032; Date: 26-Jan-1995 (Vol. 1.60, p. 58-64)

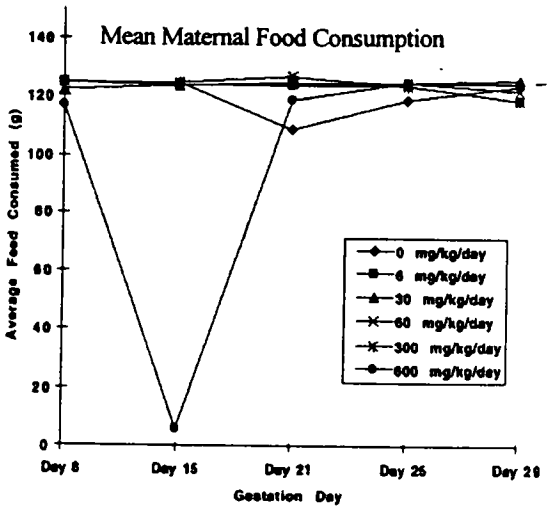
Study Nº: EX4310
Report Nº: PSA-95S-30-EX4310
Study Aim: To evaluate the potential toxic effects of SC-58635 on fetal viability in rabbits
Compound: SC-58553 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Dose & Route: 6, 30, 60, 300, and 600 mg/kg/day, 10 ml/kg for 12 days by gavage
Control vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O, 10 ml/kg
Animals: 36 nulliparous ♀ New Zealand White rabbits, approximately 5 mon of age; Strain Hra:(NZW)SPF; Weight: g; 6/group
Study Location: G.D. Searle, Skokie, IL
Study Date: 11/28/94 - 12/20/94
Compliance with GLP/QAU: No
Study Design: Pregnant rabbits, 6 groups of 6, were orally administered with SC-58635 (6, 30, 60, 300, or, 600 mg/kg) or vehicle via gavage for 12 days from Gestation Days 7-18. Animals were examined daily for mortality and clinical signs starting on Gestation Day 7. Body weights were measured on Gestation Days 0, 7, 10, 13, 16, 19, 24, and 29. Food consumption was measured for the 24 hr interval on Gestation Days 7-8, 14- 20-21 24-25, and 28-29. Blood samples was taken on Gestation Days 7 and 17 at selected time points for the determination of plasma SC-58635 levels. All surviving animals were sacrificed on Gestation Day 29. Gross pathological examine was performed and the reproductive tracts were evaluated to acquire the numbers of corpora lutea, implantations, resorptions, and live and dead fetuses. All fetuses were individually weighed and examined.

Results:

- Clinical Signs and Mortality - No treatment-related mortality occurred at any dosage level. One rabbit from each of 6 and 300 mg/kg/day group died from gavage error on Gestation Day 11. Post mortem examinations showed foamy, fluid-filled lungs. One female in 600 mg/kg/day group aborted on Gestation Day 24. Two rabbits in the same group showed clinical sings of red materials.

- Body Weight and Food Consumption - Decreased body weights during treatment period, Gestation Days 7 - 18 and a marked decrease in food consumption between Gestation Days 14-15 were noted in rabbits receiving SC-58635 600 mg/kg/day group as depicted in the following figure.





- Female Reproductive Parameters - It appeared that no drug related effects on the mean numbers of corpora lutea, implantations, resorptions, fetal weights and live or dead fetuses were noted in groups of rabbits receiving ≤300 mg/kg/day. In the 600 mg/kg/day group, significantly increased post-implantation losses ($p \leq 0.003$) and decreased live fetuses ($p \leq 0.014$) were noted. External examination of fetuses revealed no SC-58635 treatment associated changes. In conclusion, SC-58635 had significant maternal toxicity and embryo-fetal toxicity at the level of 600 mg/kg/day by the evidence of weight losses, reduced food consumption, clinical signs, significantly higher post-implantation loses, and significantly reduced live fetuses.
- PK- SC-58635 could be detected in all plasma samples indicating that it was systemically available at all dosage levels. Mean plasma SC-58635 concentrations on treatment Days 1 and 11 (Gestation Days 7 and 17) are listed in the following table.

Dose (mg/kg)	Plasma SC-58635 Concentration (μg/ml)							
	2 hr		3 hr		4 hr		24 hr	
	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11
6	0.108	0.167	0.132	0.155	0.125	0.173	-	0.0132
30	0.49	0.454	0.535	0.462	0.559	0.673	0.0591	0.0663
60	0.838	0.655	1.17	1.02	0.837	0.737	0.227	0.212
300	1.64	2.65	1.94	3.45	1.89	2.97	1.69	1.95
600	2.1	10.1	2.83	8.49	2.54	10.2	2.64	6.25

2.4.2.4. A Pilot Study Of SC-58635 In Rabbits, Document No.: PSA95S-30-EX4309; Date: 20-Feb-1995 (Vol. 1.60, p. 70-85)

Included as an appendix to this report was:
Searle Memo Report Of SC-58635 Plasma Concentrations In The Pilot Study Of SC-58635 In Pregnant Rabbits, EX4309, Document No.: MRC-95S-0031; Date: 23-Jan-1995 (Vol. 1.60, p. 83-85)

Study Nº	EX4309
Report Nº	PSA95S-30-EX4309
Study Aim:	To evaluate the potential toxic effects of SC-58635 and to establish PK data for dosage selection in a range-finding study in rabbits

Compound: SC-58553 (Lot Nº 94K014-A1B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O

Dose & Route: 200, 400, and 600 mg/kg/day, 10 ml/kg for 4 days by gavage

Animals: 6 mated ♀ New Zealand White rabbits (Gestation Days 19-21) 7 months of age; Strain Hra:(NZW)SPF; Weight: g; 2/group

Study Location: G.D. Searle, Skokie, IL

Study Date: 11/7-11/1994

Compliance with GLP/QAU: No

Study Design: Female rabbits, 2/group, were given SC-58635 suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O at levels of 200, 400, or 600 mg/kg/days for 4 days by gavage. Clinical signs and mortality were monitored daily. Blood sampling was taken for plasma SC-58635 determination at approximately 2, 3, 4, and 24 hr following the first dosing and 24 hr following the last dosing. Animals were subjected to post-mortem examinations on day 5.

Results: Animals receiving 600 mg/kg/day had decreased body weights (↓ 5% on Day 5) with signs of few, soft, and small or no feces. No significant changes were attributable to the treatment at post-mortem. Plasma SC-58635 concentrations were as followings:

Dose (mg/kg/day)	Mean Plasma SC-58635 Levels (μg/ml)				
	Day 1				Day 4
	2 hr	3 hr	4 hr	24 hr	24 hr
200					
400	3.86 ± 0.86	3.46 ± 0.42	3.78[a]	3.61 ± 0.69	3.70 ± 0.78
600					

[a]Data was obtained from a single animal.

Based on data presented in the current study, SC-58635 was considered to be toxic at 600 mg/kg/day level.

2.4.2.5. A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits, Document No.: PSA95S-30-SA4342; Date: 25-Oct-1995 (Vol. 1.60, p. 86-255)

Included as an appendix to this report were:

1. Evaluation Of Plasma SC-58635 Concentrations In A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits (SA4342), Document No.: MRC95S-30-950134; Date: 24-Jul-1995 (Vol. 1.60, p. 223-245)
2. Final Report Amendment No. 1: A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits (SA4342), Document No.: P31S4342; Date: 16-Oct-1997 (Vol. 1.60, p. 249-255)

Study Nº: SA4342

Report Nº: PSA95S-30-SA4342

Study Aim: To determine the possible adverse effects on the pregnant female rabbits and on the development of the embryo and fetus following multiple oral administration of SC-58635 on Gestation Days 7-18.

Compound: SC-58635 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v), 0.1% polysorbate 80 (v/v) in dist. H_2O

Dosage & Route: 0, 60, 150, and 300 mg/kg/day, 10 ml/kg po from Gestation Day 7-18 for 12 days

Animals: New Zealand White ♀ rabbits (Hra:SPF), weighing g, months of age, 20/group

Study Location: G.D. Searle, Skokie, IL

Study Date (In-Life): 2/5/95 - 3/3/1995.

Compliance with QAU: Yes

Study Design: Pregnant female rabbits were dosed with SC-58635 at 0, 60, 150, or 300 mg/kg/day for 12 days (from Gestation Days 7-18). All animals were observed for clinical signs at least once daily. All rabbits were sacrificed on Gestation Day 29 and all maternal and fetal data were collected. Blood samples were collected on Gestation Days 7 & 19 at 1, 2, 3, 4, 8, and 24 hr post dosing. Plasma SC-58635 concentrations were determined by a validated HPLC method.

Results:

- Clinical Observations & Mortality - Two in each of 60 and 300 mg/kg groups were found dead as results of dosing errors. Reduced feces, soft stool and fecal tinted fur were seen scattered across all groups.
- Food Consumption and Body Weight - Food intake and body weight gains were comparable among treated and control animals.
- Toxicokinetics - Dose-dependent but not dose-proportional increases in C_{max} and AUC were noted on Gestation Days 7 & 19. The following table showed summarized PK parameters obtained on Gestation Days 7 & 19. C_{max} and AUC values were higher on Gestation Day 19 than those values obtained on Gestation Day 7 indicating that accumulation of SC-58635 had occurred after repeated dosing.

Parameter	60 mg/kg		150 mg/kg		300 mg/kg	
	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19
AUC (μg•hr/ml)	14.9	22.5	24.5	41.5	37.4	89.0
AUC/Dose	0.249	0.375	0.164	0.227	0.125	0.297
Cmax (μg/ml)	0.951	1.49	1.41	2.37	1.76	5.14
C_{max}/Dose	0.0158	0.0248	0.00942	0.0158	0.00585	0.0171
T_{max} (hr)	8.00	8.00	8.00	8.00	4.00	8.00

- Fetal Parameters - External and visceral fetal examination showed a slight increase in sternebrae fused of the fetuses at 150 mg/kg group. There was a slight and dose-dependent increase in the incidence of misshapen sternebrae in the fetuses at 150 and 300 mg/kg groups during skeletal examination.

	Dose (mg/kg/day)			
	Control	60	150	300
Nº. Live Fetuses Examined	177	121	153	111
Nº Litter Examined	20	17	20	16
TYPE AND NUMBER OF FETAL ALTERATIONS: (Nº of Fetuses/Nº of Litters)				
Ribs Fused (M)	1 (0.6%)/1	2 (1.7%)/1	2 (1.3%)/2	4 (3.6%)/4
Sternebrae fused (M)	1 (0.6%)/1	2 (1.7%)/2	13 (8.5%)/10	5 (4.5%)/4
Sternebrae Misshapen (V)	2 (1.2%)/2	3 (2.5%)/3	6 (3.9%)/4	5 (4.5%)/2

- Maternal Reproductive Performance - Oral administration of SC-58635, at dosages of 150 mg/kg/day, to pregnant rabbits did not have adverse effects on the average of corpora lutea, implantations, resorption and live or dead fetuses. In contrast, at the dose level of 300 mg/kg, SC-58635 caused significant decreases in the numbers of live fetuses and significant post-implantation losses (resorption and dead fetuses) as shown in the following table.

REPRODUCTIVE STATUS OF PREGNANT FEMALES AT SACRIFICE

DOSE GROUP		FETAL OBSERVATIONS: CORPORA LUTEA	IMPLANTATIONS	RESORPTIONS	LIVE FETUSES	DEAD FETUSES	PREIMP. LOSS(a)	POSTIMP LOSS(b)
CONTROL	MEAN	11.2	9.6	0.8	8.9	0.0	1.6	0.8
	IMN(c)	10.9	9.6		8.9		1.1	0.6
	STD	2.1	2.4	1.1	2.2	0.0	1.6	1.1
	N	20	20	20	20	20	20	20
60 MG/KG SC-58635	MEAN	10.2	8.1	1.0	7.1	0.0	2.1	1.0
	IMN(c)	10.0	8.3		7.4		1.4	0.7
	STD	1.8	2.2	1.5	2.3	0.0	2.6	1.5
	N	17	17	17	17	17	17	17
	P-VALUE (TREND)				.025*			
150 MG/KG SC-58635	MEAN	9.9	8.9	1.3	7.7	0.0	1.0	1.3
	IMN(c)	9.6	9.0		7.9		0.8	0.9
	STD	1.7	2.1	1.4	2.6	0.0	1.0	1.4
	N	20	20	20	20	20	20	20
	P-VALUE (TREND)				.025*			.17
300 MG/KG SC-58635	MEAN	10.9	9.5	2.6	6.9	0.1	1.4	2.6
	IMN(c)	10.4	9.4		7.2		0.9	2.1
	STD	2.7	3.0	2.0	3.2	0.3	1.8	2.0
	N	16	16	16	16	16	16	16
	P-VALUE (TREND)	(d)	.21	(e)	.018*	(e)	1.0	.001*

(a) Calculated as Corpora Lutea - Implantations
(b) Calculated as Resorptions + Dead
(c) IMN computed only for those parameters statistically analyzed
(d) Tested only for global homogeneity, p-value = .19
(e) Parameter not statistically analyzed

Therefore, the lowest no-observable-effect level (NOEL) for maternal, reproductive, and developmental toxicity in the rabbits were 300, 150 and 60 mg/kg, respectively.

2.4.3. PERINATAL/POSTNATAL STUDY

2.4.3.1. A Study Of Pre And Postnatal Development With SC-58635 By Oral Administration In The Rat, (SA 4404), Document No.: P30S4404; Date: 21-Mar-1997 (Vol. 1.61-1.64)

Included as an appendix to this report was:
Evaluation Of Plasma Concentration Data In A Study Of Pre And Postnatal Development With SC-58635 By Oral Administration In The Rat, SA4404, Document No.: M3096141; Date: 28-Oct-1996 (Vol. 1.64, p. 202-218)

Study Nº:	SA4404/95903
Report Nº:	P30S4404
Study Aims:	To examine the effects of SC-58635 on gestation, parturition and lactation in the dams and the development, survival, physical development, behavior and reproductive performance of the pups.
Compound:	SC-58635 (Lot Nº 95K010-A1A)
Vehicle:	0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) in dist. H_2O
Dosage & Route:	0, 10, 30, or 100 mg/10 ml/kg po by gavage from Gestation Day 6 to Days 21-23 post partum
Animals:	Sprague-Dawley rats, Crl:CD®(SD)BR, 12 weeks of age, weighing 212-292 g, 25 ♀/group

Study Date (In-Life): 10/2/95 - 2/20/96
Study Site:

GLP/AUC: Yes

Study Design: Group of 25 pregnant ♀ (F_0) were given SC-58635 at doses of 10, 30, and 100 mg/10 ml/kg/day from Gestation Day 6 through Days 21-23 post partum by oral gavage. F_1 generation (1/sex from each litter), weaned on Day 21 post partum, was examined for physical, reflex/sensory development, behavior and reproductive performance. All non-selected pups were subjected to a gross examination. The following observations were performed.

Group	Compound	Dose (mg/kg/day)	Nº of mated ♀
1	Vehicle Control	0	25
2	SC-58635	10	25
3	SC-58635	30	25
4	SC-58635	100	25

F_0 Generation:

- Clinical Signs and Mortality - 2x/day
- Body Weight - Gestation Days 0, 6, 9, 12, 15, 18, and 20 and Post Partum Days 0, 4, 7, 10, 14, 17 and 21.
- Food Consumption - Gestation Days 0-6, 6-9, 9-12, 12-15, 15-18, and 18-20.

F_1 Litter Observation:

- Clinical Condition - 1x/day during the lactation period.
- Body Weight - Days 4, 7, 10, 14, 17, and 21 post partum.
- Culling - On Day 4 post partum, the litter was culled to 8 pus (4♂ & 4♀)
- Physical Development - Day 1 post partum and on onward: pinna unfolding; Day 7 post partum and on onward: tooth eruption; Day 12 post partum and on onward : eye opening.
- Reflexological Development - Days 2 and on onward or 4 post partum.
- Weaning and Selection for F_1 Adult Generation - Day 21 post partum, 1♂ and 1♀ were selected from each litter to form F_1 adult generation.

F_1 Adult Observation:

- Clinical Condition - 2x/day
- Body Weight - Gestation Days 0, 6, 9, 12, 15, 18, and 20.
- Physical Development - ♀: Day 26 post partum and on onward, assessment of vaginal opening; ♂: Day 35 and on onward, assessment of preputial separation.
- Visual Function (pupillary closure and visual placing)- Day 21 post partum
- Behavior Performance -
  Motor Activity: Figure 8 mazes assessment on Days 35 (±1) and 60 (±2) post partum.
  Auditory Startle Habituation: startle habitation assessment on Day 55 (±2) post partum.
  'E' Water Maze: Days 60 and 70 post partum
- Mating Procedure - On Day 85, 1♂ and 1♀ from the same dose group were placed together for a maximum of 14 days. Vaginal lavage was examined for spermatozoa and to identify pregnancy.
- Observation at parturition - 3x/day from Gestation Day 20 for signs of parturition and any sign of dystocia.

F_2 Generation:

- Pups - On Day 0 post partum, the pus were weighed and examined for malformations, sexed and the number of alive and dead recorded.
- Clinical Condition and Mortality - 1x/day.
- Body Weight - Days 0 and 4 post partum.

Terminal Sacrifice:

F_0 and F_1 Adult Generation - Necropsy and gross pathological examination were performed. F_1 males were sacrificed immediately after the end of mating period. F_1 females that failed to mate were sacrificed 26-28 days after the end of mating period. F_0 dams were sacrificed on Days 21-

23 post partum and the number of implantation sites were recorded. F_1 dams were sacrificed on Days 4 or 5 post partum and the number of implantation sites were recorded. The following were retained in 10% neutral buffered formalin for fixation and possible future histopathological examination: animal identification, seminal vesicles, epididymides[10], testes[10], mammary glands (thoracic and inguinal), uterus, vagina, ovaries, abnormal tissues, and prostate. All digestive tracts retained as abnormal tissues of all F_0 females who died preterminally or were sacrificed in a moribund condition, and selected tissues retained as abnormal for the F_1 females in the 30 and 100 mg/kg/day treated groups were prepared for histological examination.

F_1 and F_2 Pups - Pups dying or sacrificed as malformed on or before Day 7 post partum for the F_1 generation and Day 4 post partum for the F_2 generation were placed in Bouin's fluid for subsequent examination using a modified Barrow and Taylor[11] technique. A complete necropsy was performed on pups of the F_1 generation dying or sacrificed between Days 8 and 21 post partum and postweaning F_1 generation not selected for breeding or for the determination of plasma concentrations of SC-58635.

On Day 4 or 5 post partum, any externally abnormal F_2 generation pups were examined as described above for pups dying or malformed. Externally normal F_2 generation pups were euthanized and discarded without further examination.

PK/TK:

F_0 Generation: Plasma samples were obtained from 5 dams/group for the vehicle control, 10 and 30 mg/kg/day treated groups and 4 dams/group for the 100 mg/kg/day treated group.

F_1 Generation - Plasma samples were obtained from pups that were not selected for breeding for the determination of SC-58635 plasma concentrations at terminal sacrifice.

Results:

F_0 Generation:

- Clinical Signs and Mortality - Deaths or moribund were found in 1 ♀ @ 30 mg/kg/day and 8 ♀ @ 100 mg/kg/day group with clinical findings of fur staining of the muzzle and urogenital regions, thin body condition and prominent backbone, body condition dehydrated/weak, cold to touch, decreased muscle tone, decreased activity, pale skin, shallow respiration, discharges from eyes/vagina, and firm abdominal structure. Deaths were the result of peritonitis and/or gastrointestinal lesions.
- Body Weights and Food Consumption - Similar body weights and body weight gains during gestation and lactation were seen in the control and treated groups. A dose-related, transitory, decrease in food consumption was noted for all treated groups from Gestation Days 6 to 9 (78.3, 76.3, 75.0, and 71.4 grams/animal for the control 10, 30, and 100 mg/kg/day groups, respectively).
- F_0 Reproductive Performance - A slight ↓ in the gestation index was seen in ♀ at the 30 and 100 mg/kg/day groups (95.8 and 92.0 %, respectively vs. 100% in the control group) as a result of the deaths of one pregnant animal in the 30 mg/kg/day group and 2 pregnant animals in the 100 mg/kg/day group during gestation. A significant ↓ in the mean number of live pups was observed in mid- and high-dose ♀ (15.6, 14.5 and 14.1 live pups/litter in the control, 30 and 100 mg/kg/day groups, respectively). A significant ↑ in the incidence of litters with dead pups was also observed in mid dose (5 dead pups from 23 litters) and high dose (8 dead pups from 23 litters) groups.

F_1 Generation:

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[10] Fixed with Zenker's fluid for sacrificed rats only.

[11] Barrow, M.V. and Taylor, W.J., 1969. A rapid method for detecting malformations in rat fetuses. J. Morph. 127: 291-306.

- F_1 Pups - Pup viability, body weights, survival and lactation indices were comparable across all groups and there were no treatment-related clinical observations for the F_1 generation pups. Dilation of various gastrointestinal segments, digesta changes and/or urinary bladder changes were noted in pups born to dams that were found dead or at moribund in the 100 mg/kg/day group. These observations might be secondary to the deteriorating condition of the dams.
- Visual Function - Comparable results were seen in all groups for the visual placing and pupillary closure.
- Physical Development - Pups born to dams in mid and high dose groups showed significant delayed in the mean days of preputial separation. The mean day of development of tooth eruption and the values for righting reflex, negative geotaxis and auricular startle were similar between groups.
- Behavior Assessment - No remarkable findings were attributable to the treatment.
- Reproductive Performance - There were no significant differences in the parental and maternal performance parameters (mating and fertility index, conception rate, gestation index, length of gestation, implantation sites and live birth index).

F_2 Generation:

- Viability, Clinical Signs, Body Weights and Gross Pathological Findings - No differences were found.

PK/TK: SC-58635 was absorbed and systemically available to the F_0 dams and their offspring The following table shows the range of plasma concentrations of SC-58635 seen in the dams and pups.

DOSE (mg/kg/day)	Range of Plasma Concentrations of SC-58635 (μg/ml)	
	DAMS	PUPS
10	0.175 - 0.660	<0.0250 - 0.0484
30	0.422-1.20	<0.0250 - 0.435
100	<0.0250 - 2.44	<0.0250 - 7.15

Based on the results of this study the NOAEL for the survival, physical development, behavior and reproductive performance of the F_1 ♂ and ♀ was 100 mg/kg/day as only minor changes were seen in development. The NOAEL for F_0 toxicity was 10 mg/kg/day due to mortality at 30 and 100 mg/kg/day and an increase in dead pups at 30 and 100 mg/kg/day.

2.5. GENETIC TOXICOLOGY

2.5.1. IN VITRO TESTS

2.5.1.1. An Evaluation Of The Mutagenic Potential Of SC-58635 In The Ames Salmonella/Microsome Assay, Document No.: PSA-94S-4242; Date: 18-Jul-1994 (Vol. 1.65, p. 1-23)

Study Nº: SA4242
Report Nº: PSA-94S-4242
Study Aim: To evaluate mutagenic potential of SC-58635 using Ames Salmonella/microsome assay
Compound: SC-58553 (Lot Nº C00025) dissolved in DMSO, 100 mg/ml
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate.
Vehicle Control: DMSO, 50 μl/plate
Indicator Cells: *Salmonella typhimurim* strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538
S9 Mix: Aroclor 1254-induced rat-liver S9 homogenate
Positive Control:

Chemical	S9 Mix	Tester Strains	Conc. (μg/plate)
NaN_3 (sodium azide)	-	TA1535, TA100	1
2-Nitrofluorene	-	TA 1538, TA98	2.5
ICR-191 acridine	-	TA97a	0.5
2-Aminoanthracene	+	TA97a, TA98, TA100, TA1535, TA1538	1.0

Test Article Exposure Time: 48 hr at 37ºC
Study Location: Searle Research and Development, Skokie, IL
Study Date: 5/3/94 - 5/5/94
Compliance with GLP/QAU: Yes

Results: A precipitate was observed when *Salmonella typhimurim* (all tested strains) incubated with SC-58635 at concentrations 1000 and 5000 μg/plate and colony counts were not determined at these concentrations. SC-58635 was toxic at concentrations of ≥500 μg/plate as a reduction in the number of revertants and the presence of microcolonies. Therefore, SC-58635, at concentrations up to 500 μg/plate, was not mutagenic at any concentrations under current testing system.

2.5.1.2. An Evaluation Of The Mutagenic Potential Of SC-58635 In The CHO/HGPRT Mutation Assay, Document No.: PSA-94S-4299; Date: 05-Dec-1994 (Vol. 1.65, p. 24-52)

Study Nº: SA4299
Report Nº: PSA-94S-4299
Study Aim: To evaluate mutagenic potential of SC-58635 using CHO/HGRT mutation assay
Compound: SC-58553 (Lot Nº 94K014-A1B) dissolved in DMSO
Positive Controls: ICR-191 acridine, 1 μg/ml; 3-methylcholanthrene (MCA), 1 μg/ml
Dose:
Range-Finding: 0.08, 0.27, 0.80, 2.67, 8.0, 2.67, 8.0, 26.67, 80.0, 266.67, and 800.0 μg/ml
-S9: 4, 8, 12, and 16 μg/ml
+S9: 15, 30, 45, and 60 μg/ml
Indicator Cells: CHO cells (subline K1-BH4)

S9 Mix: The 9000 x g supernatant fraction of the liver homogenate from Aroclor 1254-treated rats

Exposure Time: -S9: 20-24 hr at 37°C; +S9: 4 hr at 37°C

Study Location: G.D. Searle, Skokie, IL

Study Date: 10/5/94 - 11/4/1994

Compliance with GLP/QAU: Yes

Study Design: Cells were treated with various concentrations of SC-58635 or positive control compounds, either for 20-24 hr without metabolic activation or approximately 4 hr with metabolic activation.

Results: Results of the dose range finding cytotoxicity test in the presence or absence of metabolic activation are shown in the following table.

Compounds	Concentration (μg/ml)	Relative Cell Survival (%)	
		-S9	+S9
DMSO	1% (v/v)	100	100
SC-58635	0.08	68	94
	0.27	88	81
	0.80	82	83
	2.67	65	78
	8.00	49	81
	26.67	NC	60
	80.00	NC	NC
	266.67	NC	NC
	800	NC	NC

NC = Not cloned due to insufficient cell numbers.

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Data from the mutation experiment with or without S9 mix are presented in the following table. Apparently, under the test condition without S9 mix, the concentrations of SC-58635 used did not reach maximum condition as 47% of cell survival were observed at 16 μg/ml, the highest concentration tested[12]. Therefore, celecoxib was not mutagenic at doses up to 16 μg/ml and 45 μg/ml in the absence and presence of S9 activation, respectively.

Compounds	-S9			+S9		
	Concentration (μg/ml)	Cell Survival on Day 1 (%)	Mutant Colonies/1x10^6 Clonable Cells	Concentration (μg/ml)	Cell Survival on Day 1 (%)	Mutant Colonies/1x10^6 Clonable Cells
DMSO	1%(v/v)	100	1.5	1% (v/v)	100	1.1
ICR-191 acridine	1	27	362.8**	-	-	-
MCA	-	-	-	1	53	166.1**
SC-58635	4	78	1.7	15	80	0.6
	8	68	1.0	30	69	1.7
	12	58	3.8	45	7	0.0
	16	47	0.6	60	NC	-

** significant at p≤0.01.

2.5.1.3. An Evaluation Of The Potential Of SC-58635 To Induce Chromosome Aberrations In Vitro In Chinese Hamster Ovary (CHO) Cells, Document No.: PSA-94S-4302; Date: 17-Nov-1994 (Vol. 1.65, p. 53-92)

Study Nº: SA4302

Report Nº: PSA94S-SA4302

Study Aim: To evaluate mutagenic ability of SC-58635 to induce chromosomal aberrations in CHO-WBL cells

Compound: SC-58553 (Lot Nº 94K014-A1B) dissolved in DMSO

[12] ICH S2A Document: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, 19 July 1995.

Dose: 0.08, 0.27, 0.80, 2.67, 8.0, 2.67, 8.0, 26.67, 80.0, 266.67, and 800.0 μg/ml for range-finding study; 10, 20, and 40 μg/ml for assay condition -/+ S9 activation mixtures
Vehicle Control: DMSO, 200 μl
Positive Controls: Mitomycin C (MMC), 0.5 μg/ml; Cyclophosphamide (CP), 5 μg/ml
Indicator Cells: CHO cells (subclone WBL)
Exposure Time: -S9, 4 and 24 hr; +S9, 4 hr
Study Location: G.D. Searle, Skokie, IL
Study Date: 10/4/95 - 11/2/94
Compliance with GLP/QAU: Yes
Study Design: Cells with or without metabolic activation system (liver S9 homogenate) were treated with various concentrations of SC-58635 for 4 hr or 24 hr. Cells were washed and fresh complete culture medium was added. Twenty one to 22 hr from the beginning of dosing, colcemid (0.1 μg/ml) was added to cells for 1.5-2 hr. Cell were then collected and metaphase analysis were performed. The following parameters were calculations:

% Aberrant Cells = (Total number of cells with at least one aberration)/(Total number of cells examined per dose)x 100

Cell with >1 Aberration = (Total number of cells with two or more aberrations)/(Total number of cells examined per dose) x 100

Aberrations/cell = (Total number of aberrations)/(Total number of cells) x 100

Results: In the range finding cytotoxicity experiment, results showed that no viable cells could be found at the doses ≥80 μg/ml and precipitations occurred at doses ≥266.67 μg/ml in the presence or absence of S9. **An increase in cell endoreduplication was observed in cells treated with SC-58635 in the presence of activation mix. Higher frequency of endoreduplicated cells was noted at 30 and 40 μg/ml as shown in the following table.** The biological significance of this increasing incidence of cell abnormality is unknown.

Treatment	Dose	Cell Viability (%)			Endoreduplication (%)		
	(μg/ml)	Exp. 1	Exp. 2	Exp. 3	Exp. 1	Exp. 2	Exp. 3
DMSO	20 μl	100	100	100	0	1	0.5
SC-58635	20	100	100	116	4	-	0
	30	-	70	97	-	10	3
	40	41	46	45	14	9	17

No viable cells were noted in all experiments when cells were treated with 80 μg/ml of SC-58635. Data from the 4 hr aberration assays are shown in the following table.

Treatment	Dose	Nº Cells Scored		Abs/Cells		%Cells w/Abs		% Cells w/>1 Abs		% Cell Survival	
	μg/ml	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
DMSO	20 μl	200	200	0.010	0.000	1.0	0.0	0.0	0.0	100	100
MMC	0.5	66		≥0.667		45.5		13.6		72	
CP	5.0		71		≥0.704		43.7		18.3		55
SC-58635	10	200	200	0.000	0.010	0.0	1.0	0.0	0.0	101	107
	20	200	200	0.000	0.010	0.0	0.5	0.0	0.5	94	100
	40	200	200	0.020	0.030	2.0	1.0	0.0	0.5	49	41

2.5.2. IN VIVO TEST

2.5.2.1. An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: PSA95S-30-SA4326; Date: 10-Mar-1995 (Vol. 1.65, p. 93-139)

Included as an appendix to this report were:

1. Final Report Amendment No. 1: An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: PSA96S-31-SA4326; Date: 25-Mar-1996 (Vol. 1.65, p. 133-135)
2. Final Report Amendment No. 2: An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: P31S4326; Date: 26-Feb-1997 (Vol. 1.65, p. 136-137)
3. Final Report Amendment No. 3: An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: P33S4326; Date: 05-Mar-1997 (Vol. 1.65, p. 138-139)

Study Nº: SA4326
Report Nº: PSA95S-30-SA4326
Study Aim: To evaluate the potential of SC-58635 to induce micronuclei in the bone marrow polychromatic erythrocytes of 8 week old Sprague-Dawley rats
Compound: SC-58553 (Lot Nº 94K014-A1B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O; Cyclophosphamide (CP), 60 mg, served as positive control
Dose & Route: 150, 300, and 600 mg/kg/day for 3 days, 10 ml/kg, oral gavage
Control Vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Animals: 30♂ & 30♀ Sprague-Dawley rats, strain CD(SD)BR, ~8 weeks of age, weighing 239.6 - 262.5 g for % and 183.8 - 199.6 g for & rats
Study Location: G.D. Searle, Skokie, IL
Study Date: 12/6/1994 - 1/5/1995
Compliance with GLP/QAU: Yes
Study Design:

Group	Dose	Nº Animals
Vehicle Control	10 ml	5/Sex
Cyclophosphamide	60 mg	5/Sex
SC-58635	150 mg	5/Sex
SC-58635	300 mg	5/Sex
SC-58635	600 mg	5/Sex

Animals were randomly assigned into 5 groups of 10 (5♂ & 5♀) and orally (by gavage) received either vehicle, cyclophosphamide (60 mg/kg) or SC-58635 (150, 300, or 600 mg/kg, 10 ml/kg) once daily for 3 days. Clinical sign and mortality were monitored. Animals were sacrificed on Day 4, approximately 24 hr post last dosing. Bone marrow from tibia of each animal was extracted; four smears were prepared and stained with acridine orange. Slides were evaluated for micronuclei in polychromatic (PCE) and erythrocytes.

Results: No overt clinical signs or mortality were observed. No SC-58635 induced micronucleus formation in any treatment group. In contrast, cyclophosphamide caused significant higher incidence ($p \leq 0.01$) of micronucleus formation compared to the vehicle control. Therefore, **SC-58635 did not cause micronucleated polychromatic erythrocytes in the bone marrow of rat was not a clastogen.**

2.6. SPECIAL TOXICOLOGY STUDIES

2.6.1.1. Antigenicity Study Of SC-58635, Document No.: 95-ZOAG-0276; Date: 03-Oct-1995 (Vol. 1.53, p. 40-106)

Study Nº: JBC-95-ZOAG-0276

Study Aims: To assess the antigenic potentials of SC-58635 by Active Systemic Anaphylaxis (ASA) Reaction with ♂ guinea pigs following oral or subcutaneous sensitization, by Homologous Passive Cutaneous Anaphylaxis (HmPCA) Reaction using sera of ASA animals and by Heterologous Passive Cutaneous Anaphylaxis (HtPCA) Reaction in rats using ♂ mice sera after oral or ip sensitization.

Compound: SC-58635 (Lot Nº 94K031-A2A) in methylcellulose (MC)-Tween 80 (5:1 w/w in H_2O) for sensitization use or in polyethylene glycol (PEG) 400- H_2O (2:1 v/v) for challenge use

Dose and Route:

- ASA Reaction - Test articles were prepared as followings:
  - Oral Sensitization Preparation - SC-58635, 5 or 25 mg/3ml methylcellulose-Tween 80
  - Subcutaneous Sensitization Preparation - 25 mg/3ml SC-58635 in MC-Tween 80 and Freund's Complete Adjuvant (FCA) (1:1 v/v)
  - Challenge Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline
- Homologous Passive Cutaneous Anaphylaxis (HmPCA) Reaction - Test articles were prepared as followings
  - Challenge Solution Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline; Evans Blue 10 mg/ml in saline
  - Sera from ASA animals for Intradermal Inoculation - 1/5, 1/15, and 1/45 dilutions for sera from SC-58635 sensitized animals; 1:100, 1/300 and 1/900 dilutions for sera from BSA sensitized animals.
- Heterologous Passive Cutaneous Anaphylaxis (HtPCA) Reaction -
  Oral Sensitization Preparation - SC-58635, 5 or 25 mg/20ml methylcellulose-Tween 80
  IP Sensitization Preparation - SC-58635, 25 mg/20 ml of MC and Alum in saline (1:1 v/v); BSA, 3 mg/20 ml of MC and Alum in saline (1:1 v/v)
  Challenge Solution Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline; Evans Blue 10 mg/ml in saline.

Animals: 5-7 weeks old ♂ Crj:Hartley guinea pigs, weighing 351-388 g for ASA reaction and 477-511 g for HmPCA reaction; 9 weeks old C3H/HeNCrj ♂ mice used in HtPCA sensitization, weighing 27-29 g; and 9 weeks old ♂ Crj:CD (SD) rats used in HtPCA challenge, weighing 332-366 g.

Study Date: 4-25-95 to 10-3-95

Study Site:

GLP/AUC: Yes

Study Design:

- ASA Reaction -

Sensitization Phase						Challenge (iv) Phase		Nº Animals
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Compound	Dose (mg/kg)	
SC-58635	5	-	po	7x/week	15	SC-58635	5	5
SC-58635	25	-	po	7x/week	15	SC-58635	5	5
SC-58635	25	+	sc	2x/week	5	SC-58635	5	5
BSA	3	+	sc	2x/week	5	BSA	5	5
MC	-	+	sc	2x/week	5	MC	5	5

- HmPCA Reaction (4 hr) - Sera used for challenge were obtained from guinea pigs sensitized for ASA reaction on Day 29.

Sensitization Phase						Challenge (iv) Phase		
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Compound	Dose (mg/kg)	Nº Animals Challenged
SC-58635	5	-	po	7x/week	15	SC-58635	5	2
SC-58635	25	-	po	7x/week	15	SC-58635	5	2
SC-58635	25	+	sc	2x/week	5	SC-58635	5	2
BSA	3	+	sc	2x/week	5	BSA	5	2
MC	-	+	sc	2x/week	5	SC-58635	5	2

- HtPCA Reaction - Sera used for challenge were obtained from mice on Day 29 after 1st sensitization.

Sensitization Phase - Mice							Challenge (iv) Phase - Rat		
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Nº Animals Sensitized	Compound	Dose (mg/kg)	Nº Animals Challenged
SC-58635	5	-	po	7x/week	15	5	SC-58635	5	2
SC-58635	25	-	po	7x/week	15	5	SC-58635	5	2
SC-58635	25	+	ip	1x/week	3	5	SC-58635	5	2
BSA	3	+	ip	1x/week	3	5	BSA	3	2
MC	-	+	ip	1x/week	3	5	SC-58635	5	2

Results:

- ASA Reaction - No death occurred. Staggering gate, convulsion, rubbing nose, coughing, lacrimation, dyspnea, and lying on side position were observed in BSA positive control animals. In BSA and SC-58635 sensitized animals had signs of restlessness, trembling, rubbing nose, urination and defecation following receiving iv challenge injection of SC-58635. These responses may not be related to antibody-antigen (SC-58635), since it was also noted in the MC control animals. Results suggested that intravenous injection of SC-58635 cause noteworthy adverse reactions in the guinea pigs.
- HmPCA Reaction - Sera from SC-58635 and MC sensitized guinea pig did not cause vascular leakage lesions around inoculated sites. Contrarily, sera from BSA-sensitized animals induced cause vascular leakage lesions around inoculated sites with titers of ≥900.
- HtPCA Reaction - Sera from 2/5 mice ip sensitized with BSA caused positive leakage lesions around inoculation sites.

In conclusion, SC-58635 did not pose antigenic properties.

2.6.1.2. Dermal Sensitization Study Of SC-58635 In Guinea Pigs-Maximization Test (SA 4515), Document No.: P30S4515; Date: 06-Dec-1996 (Vol. 1.54, p.1-90).

Study Nº: SA4515 6053997
Document Nº: P30S4515
Study Aims: To assess the contact sensitization potential of SC-58635 when administered by intradermal injection and topical application in guinea pigs.
Compound: SC-58635 (Lot Nº GDS4695-042)
Dose & Route: 5% in FCA/H_2O intradermal injection for sensitization; 25% in Petrolatum dermal topical for induction and challenge
Positive Control: Hexyclcinnamaldehyde; **the positive control was not performed concurrently but within 6 months of the conduct of this study (Study Nº: '51104719, 1/8/96 to 2/5/96).**
Animals: Young adult albino guinea pigs, Crl:(HA)BR, weighing 400-508 g, 4-8 weeks of age, 20 for the test group and 10 for the control group
Dosing Date: 6/6/96 - 7/8/96

Study Site:
GLP/AUC: Yes
Study Design: The below table depicts the detailed treatment schedules for the control and test groups.

Day	Treatment Schedule	Skin Induction Site (4 cm x 6 cm area)		
		Anterior Site	Medial Site	Posterior Site
		CONTROL GROUP (10 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml Propylene Glycol	0.1 ml Propylene Glycol in FCA(1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	Petrolatum secured by an overwrap with tape for 24 hr.		
		TEST GROUP (20 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml of 5% SC-58635 in Propylene Glycol	0.1 ml of 5% SC-58635 in FCA/H_2O (1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	25% w/w SC-58635 in Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	25% w/w SC-58635 in Petrolatum secured by an overwrap with tape for 24 hr.		

The following observations were made during the study:

- Clinical Signs - 1x/day.
- Body Weight - 1x before test material application and 1x at termination of in-life phase.
- Skin Reaction - The challenge sites were examined at 24 and 48 hr following challenge application patch removal. The reactions were scored according 4-point scale: 0 = no reaction; 1 = scatter mild redness; 2 = moderate and diffuse redness; 3 = intense redness and swelling.

The test and control materials were classified according to the following scheme.

MAXIMIZATION RATINGS	
Sensitization Rate (%)[a]	Classification
0	Non-Sensitizer
>0-8	Weak Sensitizer
9-28	Mild Sensitizer
29-64	Moderate Sensitizer
65-80	Strong Sensitizer
81-100	Extreme Sensitizer

[a]Percentage of animals exhibiting a dermal reaction at challenge.

Results:

- Clinical Observations and Body Weights - One animal each in the test (Days 16 and 17) and control (Day 22) groups had soft stool.
- Dermal Reaction to SC-58635 at Challenge - No animals had reaction to the challenge application of control material or SC-58635.

The sponsor stated that based on the results, SC-58635 might not be a dermal sensitizer in guinea pigs maximization test. However, the review pharmacologist do not concur with the conclusion drawn by the sponsor as positive controls were not conducted simultaneously. Therefore, the study it self may not be valid and no conclusion can be drawn from the present study.

2.6.1.3. Primary Dermal Irritation Study Of SC-58635 In Rabbits (EPA-TSCA Guidelines) 41200179), Document No.: PSA95C-30-SA4318; Date: 26-Apr-1995 (Vol. 1.54, 91-128)

Study Nº: SA4318
Report Nº PSA-95C-30-SA4318
Study Aim: To assess the relative level of primary skin irritation of SC-58635 on rabbits under semi-occluded conditions
Compound: SC-58553 (Lot m 94K014-A2B), white powder
Dose & Route: 0.5 g (≈1.0 ml dose); skin topical application

Animals: 6♂ healthy adult New Zealand White Rabbits; Strain: Hra:(NZW)SPF; Weight: 2806 - 3487 g
Study Location:
Study Date (In-Life): 12/12/1994 - 12/15/1994
Compliance with GLP/QAU: Yes
Study Design: Each rabbit received a 0.5 g dose of SC-58635 moisturized with H2O as a single dermal application. The area of application was covered with a 2.5 cm x 2.5 cm gauge patch, loosely overwrapped with Wrap7 and secured with tape to ensure the drug in contact with the skin. At the end of 4 hr exposure, the dressing was then removed and the remaining SC-58635 was wiped from the skin. The test sites were examined and scored for dermal irritation at 4, 24, 48 and 72 hr following patch removal.

Results: There was no dermal irritation. The average of the individual animal index scores was 0.

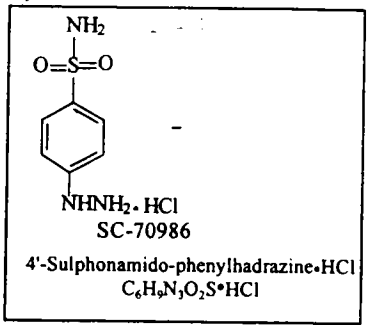
2.6.1.4. Primary Eye Irritation Study Of SC-58635 In Rabbits (EPA-TSCA Guidelines) 41200180), Document No.: PSA95C-30-SA4319; Date: 27-Apr-1995 (Vol. 1.54, p.129-171)

Study Nº: SA4319
Report Nº: PSA95C-30-SA4319
Study Aim: To assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits
Compound: SC-58553 (Lot Nº 94K014-A2B) powder
Dose & Route: 0.011 g (≈1.0 ml dose); intraocular
Animals: 6♂ Adult New Zealand White Rabbits, 3/group; Strain: Hra:(NZW)SPF; Weight: 2.0 - 3.5 kg
Study Location: , WI 53704
Study Date (In-Life): 12/14/94 - 12/17/1994
Compliance with GLP/QAU: Yes
Study Design: Each rabbit received 0.011 g (0.1 ml wt equivalent) of the drug placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and upper eyelids were held gently together for 1 sec and then released. The eyes of rabbits in group I remained unflushed immediately after treatment while the treated eyes of the rabbits in group II were flushed with lukewarm tap water for 1 min starting 30 sec after the drug applied. the treated eyes were examined for ocular irritation at 1, 24, 48, and 72 hr post treatment. Irritation was graded and recorded according to the Draize method. Sodium fluorescein was used to aid in revealing possible corneal damage at 72 post dose.

Results: Redness and swelling (slight to moderate conjunctivitis, scored 4.0) were observed in all tested eyes in group I animals at 1 hr post exposure to the drug. The conjunctival irritation disappeared and resolved completely in all animals in group I by 48 hr post treatment. Only redness (scored 3.3) were seen in all tested eyes of group II animals and the conjunctival irritation completely resolved by 24 hr post treatment. Sodium fluorescein examinations were negative for all animals 72 hr post dosing. Therefore, SC-58635 could be considered as minimally irritating according to the Kay & Calandra[13] classification criteria.

[13] Kay, J. H. and Calandra, J. C., "Interpretation of Eye Irritation Tests," Journal of the Society of Cosmetic Chemists, 1962. 13(6) :281-289.

2.7. TOXICITY OF STARTING MATERIAL IN THE SYNTHESIS OF SC-58635



2.7.1.1. Acute Oral Toxicity Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Rats (EX4503), Document No.: P30E4503; Date: 24-Feb-1997 (Vol. 1.66, p.1-50)

Study Nº: EX4503
Study Report Nº: 60401961
Study Aims: To evaluate the acute toxicity of 4-sulfonamidophenyl hydrazine hydrochloride (SC-70986), a raw material for the product of SC-58635 by oral gavage to rats.
Compound: 4-sulfonamidophenyl hydrazine (Lot Nº N00106) in dist. H_2O
Vehicle: dist. H_2O
Dose and Route: 250, 500, 1000, and 2000 mg/kg/10 ml po by gavage
Animals: Sprague-Dawley rats, Crl:CD®(SD)BR, ~7-19 weeks of age, weighing 212-289 g, 5/sex/group
Study Site:
Study Date: 4/29/96 - 6/10/96
GLP/AUC: N/A
Study Design: Rats were given a single dose of 4-sulfonamidophenyl hydrazine hydrochloride at doses of 250, 500, 1000, or 2000 mg/kg. Animals were observed for clinical signs of toxicity at 1, 2.5, and 4 hr post dosing and daily thereafter for 14 days. Mortality was checked 2x/day. Body weights were recorded on Days 0, 7 and 14. All animals were subjected to gross pathological examination. No tissues were preserved.

Results:

- Mortality - The mortality for each group and calculated LD_{50} for each sex and combined sex are listed in the below table.

Dose mg/kg	Mortality ♂	Mortality ♀	LD_{50} (95% Confidence Limit) mg/kg ♂	LD_{50} (95% Confidence Limit) mg/kg ♀
250	0/5	0/5		
500	1/5 (Day 0)	0/5		
1000	2/5 (Day 0)	5/5 (Days 0 &1)	1000 (558-1792)	707 (483-1036)
2000	5/5 (Day 0)	5/5 (Day0)	785 (556-1108)	

- Clinical Signs - Hyporeactivity, staggered gait, absence of gasping/righting reflex, prostration, clonic convulsions, thin appearance, hunched posture, red-stained face, excessive salivation, lacrimation, mydriasis, dyspnea, soft stool, wet and/or yellow-stained urogenital area were major observations. All surviving animals but 2♀ @ 500 mg/kg that had clinical signs of toxicity returned to the normal state by Day 3 post treatment.
- Body Weights - Surviving animals in each group showed similar body weight gains except one ♀ @ 250 mg/kg exhibit a weight loss of 6 g during the 2nd week of the study.
- Gross Pathology - No gross lesions were noted in the rats @ 250 mg/kg. The most apparent findings in rats that died during the study were coloration changes (brown, dark brown or dark red) of the lungs, GI tract, the nasal/oral discharge, and content of the GI tract.

2.7.1.2. Primary Eye Irritation Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Rabbits (EX4504), Document No.: P30E4504; Date: 08-Oct-1996 (Vol. 1.66, p. 51-90)

Study Nº: EX4504 60401963
Report Nº: P30E4504
Study Aims: To examine primary eye irritation study of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in rabbits.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) (Lot Nº: N00106)
Dosage & Route: 73 mg powder, ocular instillation
Animals: Adult albino rabbits Hra:(NZW) SPF, 14-18 weeks of age, 2395-2744 g, 3/group
Study Date: 5/1/96 - 5/22/96
Study Site:
GLP/AUC: N/A
Study Design: Test material, 73 mg 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986), was placed into the lower eyelid of the right eye on rabbits (2 groups of 3). The left eye served as untreated control. The treated eyes of Group 2 rabbits were flushed with water 30 sec after drug administration. Eye irritation were scored according the Draize technique at 1, 24, 48, 72, and 96 hr and 7, 14, and 24 days post instillation.

Results: Corneal and iridal involvement and moderate conjunctival irritation were noted in Group 1 animals. In contrast, only corneal involvement and slight conjunctival irritation were seen in the Group 2 rabbits (eyes were washed 30 sec after instillation of test compound). The average primary eye irritation scores are shown in the following table.

Time	Group 1 (Unflushed)	Group (H_2O Flushed)
1 hr	25.7	13.0
24 hr	23.7	11.0
48 hr	21.3	6.0
72 hr	20	4.7
96 hr	16.3	2.7
Day 07	6.3	0
Day 14	2.0	0
Day 21	0	0

2.7.1.3. Primary Dermal Irritation Study Of 4-Sulfonamidophyenyl Hydrazine Hydrochloride In Rabbits (EX4505), Document No.: P30E4505; Date: 13-Sep-1996 ((Vol. 1.66, p. 91-110)

Study Nº: EX4505 60401962
Report Nº: P30E4505
Study Aims: To examine primary skin irritation study of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in rabbits.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) (Lot Nº: N00106)
Dosage & Route: 0.5 g in 0.4 ml dist. H_2O applied to skin directly
Animals: 3♂ & 3♀ adult albino rabbits Hra:(NZW) SPF, 14-18 weeks of age, 2418-2569 g.
Study Date: 4/30/96 - 5/14/96
Study Site:
GLP/AUC: N/A
Study Design: Test material, 0.5 g of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986), was moistened with approximately 0.4 ml of dist. H_2O and was applied to the rabbit skin area that had been clipped. The area of application was cover with an 2.5 cm x2.5 cm gauze patches secured with paper tape, overwrapped with Sara Wrap and secured with Elasplast tape. The

patches were removed after 4 hr exposure to the test article. The degree of erythema and edema was recorded 30 min, 24 hr, 48 hr, 7, and 96 hr and 7 and 14 days after removal of the test material.

Results: Based on the results presented in the following table, 4-Sulfonamidophenyl hydrazine hydrochloride was considered to be a slight skin irritant under the present testing condition.

Time	Average Score
4 hr	25.7
24 hr	23.7
48 hr	21.3
72 hr	20
96 hr	16.3
Day 07	6.3
Day 14	2.0

2.7.1.4. Dermal Sensitization Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Guinea Pigs-Maximization Test, Document No.: P30E4506; Date: 24-Feb-1997 (Vol. 1.66, p. 111-198)

Study Nº: EX4506/ 60401964
Report Nº: P30E4506
Study Aims: To determine the contact sensitization potential of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in guinea pigs.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986)(Lot Nº: N00106)
Dosage & Route: 0.1 ml of 5% SC-70986 in sterile H_2O or FCA/H_2O (1:1) intradermal injection for sensitization and 25% w/w SC-70986 in Petrolatum directly applied to skin for induction and challenge.
Animals: adult albino guinea pigs Crl:(HA)BR, 4-8 weeks of age, 357-494 g, 20 for the test group and 10 for the control group.
Study Date: 5/3/96 - 6/8/96
Study Site:
GLP/AUC: N/A

Study Design:

Day	Treatment Schedule	Skin Induction Site (2 cm x 4 cm area)		
		Anterior Site	Medial Site	Posterior Site
		CONTROL GROUP (10 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml Sterile H_2O	0.1 ml H_2O in FCA(1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	Petrolatum secured by an overwrap with tape for 24 hr.		
		TEST GROUP (20 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml of 5% SC-70986 in Sterile H_2O	0.1 ml of 5% SC-70986 in FCA/H_2O (1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	25% w/w SC-70986 in Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	25% w/w SC-70986 in Petrolatum secured by an overwrap with tape for 24 hr.		

FCA = Freund's Complete Adjuvant

The following observations were made during the study:

- Clinical Signs - 1x/day.
- Body Weight - 1x before test material application and 1x at termination of in-life phase.
- Skin Reaction - The challenge sites were examined at 24 and 48 hr following challenge application patch removal. The reactions were scored according 4-point scale: 0 = no reaction; 1 = scatter mild redness; 2 = moderate and diffuse redness; 3 = intense redness and swelling.

The test and control materials were classified according to the following scheme.

MAXIMIZATION RATINGS	
Sensitization Rate (%)[a]	Classification
0	Non-Sensitizer
>0-8	Week Sensitizer
9-28	Mild Sensitizer
29-64	Moderate Sensitizer
65-80	Strong Sensitizer
81-100	Extreme Sensitizer

[a]Percentage of animals exhibiting a dermal reaction at challenge.

Results:

- Clinical Observations and Body Weights - The test group had reduced stool (8/20) and thin appearance (3/20). The test group had less body weight gains than the control group.
- Dermal Reactions - Mild to intense skin reactions were noted in all animals in the test group after challenge. Some animals (12/20) in the test group showed subcutaneous hemorrhaging, necrosis, and desquamation in the test sites following challenge. None of control animals had response to the challenge.

Based on the findings from this study, 4-sulfonamidophenyl hydrazine hydrochloride (SC-70986) was considered as an extreme dermal sensitizer in guinea pigs.

2.7.1.5. An Evaluation Of The Mutagenic Potential Of SC-70986 In the Ames Salmonella/Microsome Assay (EX4641), Document No.: P30E4641; Date: 14-May-1997 (Vol. 1.66, p. 199-228)

Study Nº: EX4641
Report Nº: P30E4341
Study Aims: To evaluate SC-70986, a raw material for the product of SC-58635, for potential mutagenic activity in the *Salmonella*/microsomal Ames assay.
Compound: SC-70986, 4-sulfonamidophenyl hydrazine HCl, (Lot Nº N00106) in H_2O, 100 mg/ml
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate
Vehicle Control: H_2O
Test Cells: *Salmonella typhimurium*: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535.
Positive Control:

Chemical	S9 Mix	Tester Strains	Conc. (μg/plate)
NaN_3 (sodium azide)	-	TA1535 and TA100	1
2-aminoanthracene	-	TA98	2.5
	+	TA97a, TA98, TA100, and TA1535	1.0
ICR-191 acridine	-	TA97a	0.5
Cumen Hydroperoxide	-	TA102	100
Danthron	+	TA102	50

Test Article Exposure Time: 48 hr at 37°C
Study Site: Searle Research and Development, Skokie, IL.
Study Date: 4/9 - 4/11/97
GLP/QAC Compliance: No

Results: SC-70986, up to 5000 μg/plate, was not toxic to *Salmonella typhimurium* (all tested strains). Significant increases in the number of revertant colonies were observed in all tested strains except TA1535. The concentrations of SC-70986 that caused significant increases the number of

revertant colonies are presented in the following table. Based on these data, it can be concluded that SC-70986 is mutagenic with all strains except TA1535 under the current testing condition.

Test Strain	S9 Mix	Concentration (μg/plate)
TA97a and TA102	-	≥50
TA97a	+	≥100
TA98 and TA100	+/-	5000

3. ADME

3.1. ABSORPTION PHARMACOKINETICS, SERUM $T_{½}$

3.1.1. RAT

3.1.1.1. The Pharmacokinetics And Metabolism Of SC-58635 Following Single Intravenous Dose Administration To The Rat (6127-220), Document No.: MRC-94S-0145; Date: 28-Nov-1994 (Vol. 1.67, p. 1-101)

Report Nº: MRC-94S-0145
Study Aim: To evaluate pharmacokinetics and metabolism of SC-58635 following a single intravenous dose administration to the rat
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 1 mg/kg, 2 ml/kg iv bolus via the tail vein over 1 min
Animals: 15♂ & 15♀ Sprague Dawley [Hla®(SD)CVF®] rats, weighing g, age weeks
Study Location:
Compliance with GLP/QAU: N/A
Study design: Animal group allocation, dose levels and sampling schedules are as follows.

Group (Animal Nº)	Dose (mg/kg)	Route	Sample Type	Sampling Time
I (12♂ &12♀)	1	IV	Plasma	5 , 15, 30, and 60 min, 2, 4, 8, and 24 hr post dosing
II (3♂ & 3♀)	1	IV	Urine, Feces	predose (-24-0 hr), 0-24, 24-48, 48-72, 72-96, 96-120 hr post dosing

Animals were fasted overnight prior to dosing until approximately 4 hours post administration. Animals in group I and II were sacrificed at 48 hr and 120 hr post dosing, respectively. Blood samples were collected from jugular vein into heparinized tubes. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice. Plasma concentrations of SC-58635 were determined by the analysis.

Results: The mean pharmacokinetic parameters are summarized in the following table. The clearance of SC-58635 in the female rats was much slower than that in the male rats (1.90 vs 7.76 ml/min•kg).

	$T_{½}$ (hr)	Clp (ml/min•kg)	VC (l/kg)	$AUC_{0-\infty}$ (μg•hr/ml)
♂	3.73	7.76	2.51	2.15
♀	14	1.9	2.42	8.38

The excretions of SC-58635 and its metabolites in the urine and feces are shown in the following table. Very small percentage of SC-58635 was excreted following IV administration indicating that SC-58635 was eliminated by hepatic metabolism.

Sample	Time (hr)	% SC-58635		% SC-60613		% SC-62807	
		♂	♀	♂	♀	♂	♀
Urine	0 - 24	0.50	0.40	0.70	0.79	98.6	97.2
Feces	0 - 24	0.79	0.00	3.62	3.38	94.0	94.4
	24 - 48	2.69	1.77	0.69	8.59	86.2	88.9

	48 - 72	-	1.88	-	8.26	-	84.0

3.1.1.2. Pharmacokinetics And Metabolism Of SC-58635 In Rat, Document No.: MRC-94S-0226; Date: 19-Jan-1995 (Vol. 1.67, p. 102-143)

Report Nº: MRC-94S-0226
Study Aim: To evaluate pharmacokinetics of SC-58635, a potent and highly selective cyclooxgenase-2 (COX-2) inhibitor in rats
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1
Dosage & Route: 2 mg/ml for iv bolus and oral solution; 0.4 mg/ml for SC-58635 po solution
Animals: ♂ Sprague Dawley rats, weighing ~0.3 kg, 3/group
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A

Results: SC-58635 was given to rats, 3/group, by tail vein injection or gavage. Blood samples were collected from each rat by retroorbital bleed into heparinized tubes. SC-58635 was administrated by gavage at 2 mg/kg in the same vehicle. Feces and urine samples were collected in some cases. Results showed that the peak plasma concentration (C_{max}) following the 10 mg/kg oral dose to the rat was 2.01 µg/ml and was reached at 3 hr (T_{max}). The AUC was 18.5 µg•hr/ml and systemic availability of SC-58635 following oral solution doses was 64.5%. Plasma elimination half-life and total plasma clearance rate of SC-58635 were 3.49 hr and 5.81 ml/min/kg, respectively. At two hr following a 2 mg/kg oral dose,]SC-58635 could be detected in liver (9.98%), skin (8.15%), muscle (23.7%) and fat (15.9%). Little or no radioactivity remained in tissues or plasma 7 days post dosing. After 48 hr, plasma radioactivity was less than twice background. $T_{½}$ was 3.72 hr. Total excretion time seemed to be 120 hr. The recovery from urine and feces (0-168 hr) was 7.22% and 93.4%, respectively. The pharmacokinetic parameters of SC-58635 in male rats are presented in the following table.

Route	Dose mg/kg	C_{max} µg/ml	T_{max} hr	$AUC_{0-\infty}$ (µg•hr/ml)	Clp ml/min•kg	V_D ml/kg	BA %	$T_{½}$ hr
Oral	10	2.01	3	18.5	NA	NA	64.5	3.67
Oral*	2	0.599	3	NA	NA	NA	NA	3.72
IV	10	4.87	NA	28.7	5.81	1860	NA	3.49

*Radioactive Dose
NA = Not Applicable

Two metabolites of SC-58635 were identified based on analysis, the benzylic hydroxylated (SC-60613) and corresponding carboxylic acid (SC-62807) analogues. Following oral intake of [^{14}C]SC-58635, the majority of metabolites in the plasma appeared to be SC-60613; whereas, SC-62807 was found to be the major metabolites in the urine and feces. Rat liver microsome metabolized SC-58635 in vitro quicker than human hepatic microsomes, and in both cases SC-60613 was the major metabolite. Pharmacokinetic-pharmacodynamic correlation was performed in the Lewis rat adjuvant arthritis model. The approximate SC-58635 C_{max} (3 hr) at the ED_{80} dose (1.43 mg/kg/day, measured on Day 10) was 0.453 µg/ml. Approximate C_{max} (on Day 10) in the adjuvant arthritis model during bid dosing of 0.3, 1, 3, 10, 30 and 100 mg/kg were 0.144, 0.317, 0.509, 1.94, 3.73 and 7.44 µg/ml, respectively.

3.1.1.3. The Plasma Concentrations Of SC-58635 At The ED_{80} For Adjuvant Arthritis In The Rat, Document No.: M3096294; Date: 06-Jun-1997 (Vol. 1.67, p. 144-169)

Report Nº: M3096294

Study Aim: To determine the AUC of SC-58635 at the ED_{80} in the rat adjuvant arthritis model
Compound: SC-58635 (Lot Nº: E90077) in 0.5% methylcellulose, 0.1% polysorbate 80
Dose & Route: 0.7 mg/kg bid po (by gavage) with 12 hr apart for 7 days , and a single dose on Day 8.
Animals: 12♂ healthy Charles River rats, 12♂ healthy Lewis rats, and 8♂ Lewis rats with adjuvant-induced arthritis, weighing ~165-393 g
Study Site: Searle Research and Development, Skokie, IL.
Compliance with GLP/QAU: N/A
Blood Collection: Blood was collected at 0.5, 1, 2, 3, 4, 8, 12 and 24 hr post dose on Day 8. Analysis of Plasma SC-58635

Result: Mean concentration of SC-58635 in plasma and PK parameters after oral administration of SC-58635 to male Charles river rats, Lewis rats and Lewis rats with adjuvant-induced arthritis are shown in the following table.

Time (hr)	PLASMA CONCENTRATION (SC-58635 μg/ml)		
	Charles River Rats	Lewis Rats	Arthritis Lewis Rats
0.5	0.0852	0.104	0.086
1	0.0968	0.133	0.118
2	0.0922	0.118	0.162
3	0.115	0.108	0.156
4	0.0948	0.128	0.152
8	0.0249	0.0342	0.0565
12	0.0162	BDL	0.0406
24	BDL	BDL	0.0393
PK PARAMETERS			
T_{max} (hr)	3	1	2
C_{max} (μg/ml)	0.115	0.133	0.162
AUC_{0-24} (μg•hr/ml)	1.38	1.67	2.29

BDL = Below Detection Limit (0.01 μg/ml)

3.1.1.4. Evaluation Of The SC-58635 Plasma Concentration Data Following Multiple Dose Administration To The Rat, MRC-94S-0230, Document No.: MRC-94S-0230; Date: 16-Nov-1994 (Vol. 1.67, p. 170-213)

Study Nº: SA4261
Report Nº: MRC-94S-0230
Study Aim: To assess the short term toxicity of SC-58635 administered daily by oral gavage to rats for 4 weeks and the reversibility of effects after 4 weeks without treatment
Compound: SC-58635 (Lot Nº GDS-2977-158) in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route: 20, 40, 80, 400 and 600 mg/kg, 10 ml/kg by oral gavage
Control Vehicle: 0.5% methylcellulose and 0.1% Tween 80
Animals: 66♂ & 66♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR VAF/Plus®, 5 wk of age, weighing from 126.7-175.4 g for ♂ and 111.8-143.2 g for ♀; 10-15/sex/group for toxicity study and 3/sex/group for PK assessment.
Study Location:
Compliance with GLP/QAU: Yes
Study Design: Animal grouping and dosage assignments were listed as followings:

Group		SC-58635 (mg/kg)	Nº of Animals
TOXICITY STUDY			
1	Control	0	15/sex

2	Low	20	10/sex
3	Mid	80	10/sex
4	Mid-high	400	15/sex
5	High	600	10/sex
PK ASSESSMENT			
6	Mid-high	400	3/sex
7	High	600	3/sex

On Days 1 and 26 of dosing the rats were dosed with SC-58635. The rats were dosed with unlabelled SC-58635 on the intervening doses. Blood was collected from all dose groups at 0.5, 1, 2, 3, 4, 6, 8 and 24 hr on Day 1 and Day 26 of dosing. The concentration of SC-58635 in plasma was determined using a validated high performance liquid chromatography . The analysis for plasma SC-58635 levels was conducted at G.D. Searle, Skokie, IL.

Results: SC-58635 was absorbed and systemically available. In male rats, systemic exposure to SC-58635 increased with dose over the dose range of 20 to 600 mg/kg except at the 600 mg/kg dose group. It appeared that maximal exposure to SC-58635 was achieved between 400 and 600 mg/kg in the male rats. The systemic exposure to SC-58635 increased with dose over the dose range of 20 to 600 mg/kg in the female rats. However, this increase was not dose proportional. The C_{max} and AUC values for female and male rats on Day 26 were on average lower than those on Day 1, indicating that induction of SC-58635 metabolism had occurred after repetitive dosing. A gender differences in the metabolism was noted as higher C_{max} and AUC values were observed in the females. The mean PK parameters on Days 1 and 26 are listed in the following table.

PK Parameters	Sample Day	Dose (mg/kg/day)											
		20			80			400			600		
		♂	♀	♂ + ♀	♂	♀	♂ + ♀	♂	♀	♂ + ♀	♂	♀	♂ + ♀
T_{max} (hr)	Day 1	3.00	3.00	3.00	8.00	8.00	8.00	3.00	8.00	8.00	6.00	8.00	8.00
	Day 26	2.00	6.00	2.00	2.00	2.00	2.00	4.00	4.00	4.00	4.00	8.00	3.00
C_{max} (μg/ml)	Day 1	2.597	3.437	3.017	5.193	7.643	6.418	10.283	12.3	10.697	6.713	13.9	10.06
	Day 26	1.573	2.63	1.973	3.087	5.55	4.318	5.853	9.6	7.727	5.533	16.2	9.825
AUC_{0-24} (μg•hr/ml)	Day 1	30.261	41.845	36.053	73.214	117.542	95.378	195.925	244.789	220.357	97.591	275.885	186.738
	Day 26	19.173	35.997	27.585	29.737	82.002	55.87	60.718	158.938	109.828	58.188	314.51	186.349

3.1.1.5. Evaluation Of Plasma Concentration Data In A Pharmacokinetic Study In Female Rats During Pre-Mating And Early Pregnancy With SC-58635 (M2097202), Document No.: M3097339; Date: 02-Dec-1997 (Vol. 1.67, p. 214-360)

Report Nº: M3096294

Study Aim: To determine the AUC of SC-58635 at the ED_{80} in the rat adjuvant arthritis model

Compound: SC-58635 (Lot Nº: 95K010-A1A) in 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 (w/v)

Dose & Route: 5, 15, 30 and 50 mg/kg, po for at least fourteen days prior to mating, throughout the mating period and through Gestation Day 7.

Animals: ♀ Charles River CrlCD®BR,

Study Site:

Compliance with GLP/QAU: N/A

Blood Collection: Blood was collected from 3 rats/dose at 0.5, 1, 2, 4, 8, and 24 hr post dose on Days 1 and 23 (Gestation Day 7). Analysis of Plasma SC-58635 was Performed by assay. Assay sensitivity was 0.0250 μg SC-58635/mL for a 0.300 ml sample without dilution.

Result: Following oral gavage administration to CrlCD®BR female rats, SC-58635 was absorbed and systemically available. The mean PK parameters (n=3) are shown in the following table. The plasma SC-58635 C_{max} and AUC values were similar on Days 1 and 23, indicating that repetitive dose administration at 5, 15, 30 and 50 mg/kg/day do not alter the pharmacokinetics of SC-58635.

Day of Dosing	Dose (mg/kg/day)	Tmax (hr)	C_{max} (μg/ml)	C_{max}/Dose	AUC_{0-24} (μg•hr/ml)	AUC/Dose
1	5	2	1.84	0.368	25.6	5.11
	15	8	3.59	0.239	57.6	3.84
	30	8	3.96	0.132	70.6	2.35
	50	8	5.93	0.119	95.7	1.91
23 (Gestation Day 7)	5	2	1.63	0.327	23.3	4.66
	15	2	3.35	0.224	47.2	3.15
	30	4	5.17	0.172	63.3	2.11
	50	8	5.25	0.105	90.9	1.82

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3.1.2. GUINEA PIG

3.1.2.1. Pharmacokinetics And Metabolism Of SC-58635 In Dog And Guinea Pig, Document No.: MRC-94S-0227; Date: 19-Jan-1995 (Vol. 1.67, p. 361-377)

Report Nº MRC-94S-0227

Study Aim: To evaluate pharmacokinetics and metabolism of SC-58635 following intravenous infusion and oral administration of solution and capsule

Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v

Dosage & Route: 0.5 & 5 mg/kg with 0.5 & 5 mg/ml iv and 5 mg/kg oral for used in dog
0.6 & 6 mg/kg with 0.12 & 1.2 mg/ml iv for used in guinea pig

Animals: ♀ Beagle dogs, weighing 9 -13 kg and ♂ Hartley guinea pigs, weighing 0.4 -0.5 kg.

Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077

Compliance with GLP/QAU: N/A

Experimental Design: Female dogs and male guinea pigs, two animals per group, were intravenously infused with two different dosages (0.5 & 5 mg/kg for dogs and 0.6 & 6 mg/kg for guinea pigs) of SC-58635 over a period of 15 min with a 15-30 min interval between two infusions. Female dogs were also given SC-58635 with doses of 5 mg/kg oral solution and oral capsule with neat chemical inside. Multiple blood sampling were performed and concentrations of SC-58635 and it's metabolites were determined by the method.

Results: The peak plasma levels and systemic availability of SC-58635 in female dogs and male guinea pigs as well as other pharmacokinetic parameters are summarized in the following table.

Species	Dose mg/kg	Route	C_{max} µg/ml	T_{max} µg/ml	AUC (0-∞) µg•hr/ml	C_L ml/min•kg	V_D ml/kg	BA %	$T_{½}$ hr
Dog	5	oral[a]							
Dog	5	oral[b]							
Dog	0.5, 5	iv							
G. pig	0.6, 6	iv							

[a] Solution in PEG-400:H_2O (2:1,, [b] Neat chemical in cap..ule; N/A = Not applicabl .

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Elimination rate of SC-58635 in guinea pig appeared to be more rapid compared to the dog and rat. The order plasma $T_{½}$ of SC-58635, pyrazole-type COX-2 inhibitor, in dog, rat and guinea pig was dog>rat>guinea pig indicating differences in rate or type of metabolism in these species. The systemic bioavailability of SC-58635 following oral administration to the dog with neat chemical in gelatin capsule was significantly lower compared to the oral solution (16.9% vs 57.1%).

3.1.3. DOG

3.1.3.1. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous And Oral Administration To The Male And Female Beagle Dog (An Exploratory Study), Document No.: MRC-94S-0133; Date: 18-Nov-1994 (Vol. 1.68, p. 1-114)

Report Nº MRC-94S-0133
Study Aim: To evaluate pharmacokinetics and metabolism of SC-58635 following intravenous bolus (1 & 15 mg/kg) and oral administration in a nonrandomized cross-over design to ♂ & ♀ beagle dogs
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 1 & 15 mg/kg, 1 ml/kg iv and 1 mg/kg po
Animals: 3♂ & 3♀ Beagle dogs, weighing kg, 6 (3♂ & 3♀)/group
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Study Design: The study design (a nonrandomized cross over), dose levels and sampling schedules were presented in the following table. Animals were fasted 15 to 20 hr prior to dosing until approximately 4 hours post administration. Each dose was given once to each animal as a solution in PEG-400:H_2O (2:1, v/v) with a washout period of at least 3 weeks between administration of each dosage form. Blood samples were collected by venipuncture according to the schedules listed in the above table. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice. Plasma concentrations of SC-58635 were determined by the analysis.

Group	Dose (mg/kg)	Route	Sample Type & Sampling Time	
			Plasma	Urine & feces
I[a] (3♂ & 3♀)	1	IV	2, 5 , 15, 30, and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 and 48 hr	-18 - 0, 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, and 144 - 168 hr
II[a] (3♂ & 3♀)	15	IV		
III (3♂ & 3♀)	1	oral	15 and 30 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24 and 24 hr	

[a] Only plasma samples were collected during this period of study.
[b] This is a non-randomized study and same animals were used in Group I, II & III.

Results: The results of this PK study were summarized as following:

- Considerable variations were seen in the K_m and V_{max} estimated in these study with the K_m ranging from µg/ml and V_{max} ranging from mg/kg/hr.
- The absolute biovailabilities of SC-58635 in both male and female dogs were 85.9 ± 20.7 and 74.4 ± 5.6, respectively.
- The pattern and route of eliminations were similar in male and female dogs following either oral or iv administration of SC-58635.
- SC-58635 was eliminated by metabolism followed by excretion of the metabolites in bile and urine. The majority metabolites of SC-58635 were excreted in urine and feces. The radioactivity in the metabolites excreted in urine and feces following 1 mg/kg either oral or iv administration were shown in the table listed below.

Sample	Route	(%)	SC-58635 (%)	SC-60613 (%)	SC-62807 (%)
Urine	iv	4.22	0.00741	0	2.67
	Oral	3.05	0.0134	0.0271	2.07
Feces	iv	90.5	0	0	60
	Oral	91.4	0	1.33	84.1

The mean plasma levels ± SEM of SC-58635 in male and female dogs and pharmacokinetic parameters following iv and oral administration at a dose of 1 mg/kg are summarized in the following two tables.

IV Administration (1 mg/kg)			Oral Administration (1 mg/kg)		
PK Parameters	♂	♀	PK Parameters	♂	♀
α (hr^{-1})	13.3 ± 12.1	7.87 ± 5.19	T_{max} (hr)	0.667 ± 0.167	1.00 ± 0.59
$\alpha_{1/2}$ (hr)	0.288 ± 0.26	0.334 ± 0.244	C_{max} (μg/ml)	0.553 ± 0.070	0.309 ± 0.015
β (hr^{-1})	0.203 ± 0.073	0.246 ± 0.083	$AUC_{0-\infty}$ (μg•hr/ml)	2.118 ± 0.465	1.565 ± 0.321
$\beta_{1/2}$ (hr)	3.92 ± 1.41	4.09 ± 1.92	BA (%)	85.9 ± 20.7	74.4 ± 5.6
C_L (ml/min/kg)	10.0 ± 2.90	7.98 ± 2.00			
V_D (l/kg)	2.30 ± 0.32	2.30 ± 0.59			

3.1.3.2. The Systemic Availability And Excretion Of SC-58635 Following Oral Administration Of Test Article In Capsule And Suspension Forms To The Female Dog (A Pilot Study), Document No.: M3094124; Date: 02-May-1996 (Vol. 1.68, p. 115-140)

Report Nº M3094124

Study Aim: To determine the systemic availability of SC-58635 following administration of the drug to the dogs as a suspension and in capsule form.

Compound: SC-58635 (Lot Nº C00025) in capsule and [redacted] SC-58635 (Lot Nº GDS3168-171) suspension in 0.5% methylcellulose/1% polysorbate 80/H_2O

Dosage Route: 20 mg/kg po

Animals: 2 female beagle dogs, weighing 9.2 and 11.3 kg, respectively.

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.

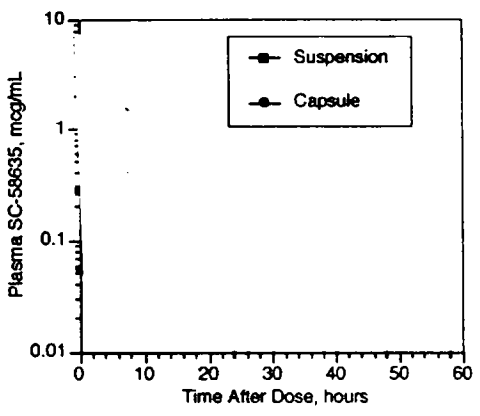
Compliance with QAU: N/A

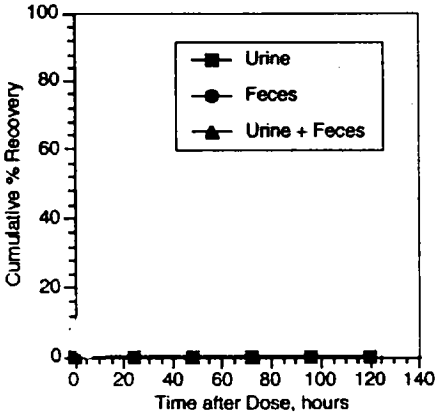
Sample Collection:

- Blood - 0, 15, 30 and 45 min, 1, , 1.5, 2, 2.5, 3, 4, 5, 6, 8, 24, and 48 hr post dosing.
- Urine and Feces - Urine and fecal samples were collected for consecutive 24 hr periods: -18-0, 0-24, 24-48, 48-72, 72-96, and 96-120 hr.

Results:

Plasma SC-58635 concentrations in a ♀ dog following a single oral dose of 90 mg/kg SC-58635 as neat chemical in a gelatin capsule or as suspension are depicted in the following figure (left panel). Cumulative of radioactivity in urine and feces in a female dog following oral administration of SC-58635 suspension 0.5% methylcellulose/1% polysorbate 80/H_2O are presented in the following figure (right panel).



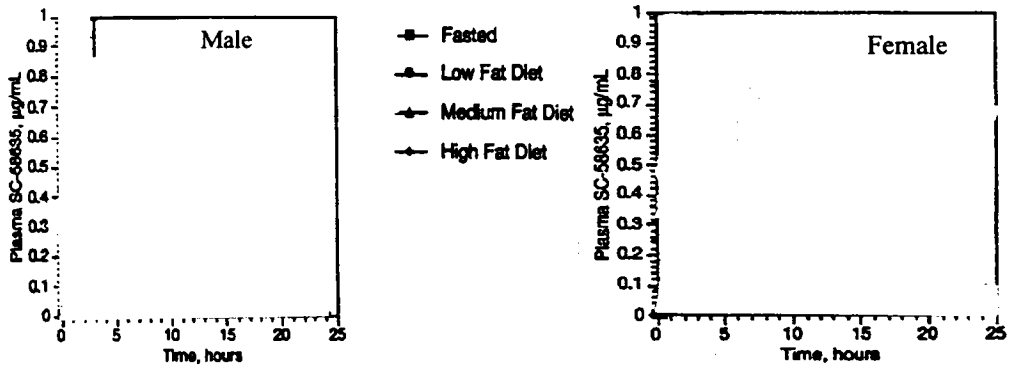


3.1.3.3. Plasma Concentrations Of SC-58635 In Dogs After Oral Administration Of SC-58635 With And Without Food, Document No.: MRC-95S-0047; Date: 13-Oct-1995 (Vol. 1.68, p. 141-188)

Report Nº MRC95S-0047 (6127-234)
Study Aim: To determine the plasma concentrations and PK following a single capsule administration of SC-58635 when administered with varying amount of dietary fat to beagles.
Compound: SC-58635 in gelatin capsule
Dosage Route: 5 mg/kg po
Animals: Beagle dogs (3♂ & 3♀), months of age, weighing kg
Study Location:
Compliance with QAU: Yes
Experimental Design:

Study Phase	Dose (mg/kg)	Diet	Nº of Dogs
1	5	Fasted	3♂ & 3♀
2	5	Low Fat	3♂ & 3♀
3	5	Medium Fat	3♂ & 3♀
4	5	High Fat	3♂ & 3♀

Results: Mean plasma SC-58635 in ♂ and ♀ dogs following a single oral dose, 5 mg/kg, administration under various diet condition are depicted in the following figure.



T_{max} and C_{max} were increased when SC-58635 was administered with food despite of the fat contents. The mean PK parameters following oral administration of 5 mg/kg to the dogs were enlisted in the following table.

Diet	C_{max} (µg/ml)		T_{max} (hr)		AUC_{0-24} (µg•hr/ml)	
	♂	♀	♂	♀	♂	♀
Fasted	0.356	0.364	1.5	7.5	1.89	3.22
Low Fat	0.712	0.775	3.0	3.67	5.63	5.58
Medium Fat	0.706	0.631	5.33	4.67	5.07	5.07
High Fat	0.737	0.808	6	5.33	6.64	6.66

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3.1.3.4. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To The Female Dog (A Pilot Study), Document No.: M3094152; Date:07-May-1996 (Vol. 1.68, p. 189-219)

Report Nº M3094152
Study Aim: To determine plasma concentrations of SC-58635 following administration of the compound to dog in several different capsule formulation.

Compound: SC-58635 in different formulated gelatin capsules
Formulation 1:
Formulation 2:
Formulation 3:
Formulation 4:
Dosage & Route: Single dose of 5 mg/kg po
Animals: Healthy ♀ dogs, 8.5-11.9 kg, 3/group
Study Location: G.D. Searle, Skokie, IL
Compliance with QAU: Not Indicated.
Study Design: This was a nonrandomized crossover study. There was a 7-day washout between two dosage forms of administrations.

Group	Dose (mg/kg)	Formulation Capsule	Nº of Animals
1	5	1	3
	5	3	
2	5	2	3
	5	4	

Blood samples were collected at 0 and 30 min, and 1, 1.5, 2, 2.5, 3.5, 7, and 24 hr post each dosing. Plasma SC-58635 levels were determined using an method.

Results: Plasma SC-58635 levels of dogs receiving different formulations of SC-58635 capsules are presented in the following table. It appeared that SC-58635 was systemically absorbed following oral administration of SC-58635 in the four different capsule formulations. High degree of variability in the plasma concentrations were seen among animals within each dose group.

Sampling	Plasma SC-58635 Concentration (Mean ± SEM), μg/ml			
Time (hr)	Formulation 1	Formulation 2	Formulation 3	Formulation 4
0	0.0012 ± 0.0012	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
0.5	0.149 ± 0.078	0.393 ± 0.300	0.104 ± 0.053	0.393 ± 0.178
1	0.531 ± 0.370	0.587 ± 0.196	0.352 ± 0.219	0.689 ± 0.178
1.5	0.633 ± 0.390	0.687 ± 0.123	0.487 ± 0.317	0.970 ± 0.148
2	0.652 ± 0.368	0.656 ± 0.052	0.541 ± 0.276	0.953 ± 0.062
2.5	0.596 ± 0.332	0.825 ± 0.178	0.460 ± 0.214	0.845 ± 0.076
3.5	0.675 ± 0.308	0.704 ± 0.144	0.489 ± 0.212	0.783 ± 0.164
5	0.465 ± 0.212	0.462 ± 0.101	0.324 ± 0.126	0.510 ± 0.165
7	0.335 ± 0.166	0.313 ± 0.090	0.278 ± 0.121	0.443 ± 0.155
24	0.0939 ± 0.0574	0.112 ± 0.045	0.136 ± 0.107	0.176 ± 0.083

3.1.3.5. Single IV Dose Pharmacokinetic Study In Dogs With SC-58635, Document No.: M2095295; Date: 10-Sep-1996 (Vol. 1.68, p. 220-264)

Report Nº: MRC-95C-100-950295 and M2195295 (Plasma Concentrations)
Study Nº: 700-341
Study Aim: To evaluate the *in vivo* clearance of SC-58635 when administered in a single dose iv to dogs.
Compound: SC-58635
Dose & Route: 5 mg/kg, 1 ml/kg iv
Animals: 2♂ & 2♀ beagle dogs
Study Site:
Compliance with GLP/QAU: N/A
Study Date: 12/01/95 - 02/28/96
Study Design: Two ♂ and 2♀ beagle dogs previous characterized as fast metabolizer of SC-58635 were sacrificed. Liver and salivary glands were collected from each animal. Liver microsomes and postmitochonrial supernatants were prepared from approximately ¼ of liver for

total P450 content and protein analyses. Blood samples were collected at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, ,6, 8, 12, 24, and 48 hr post dose.

Results: The yields of total protein and microsomal protein were similar in both sexes, ranging from of liver, respectively. Similar amounts of total microsomal P450 were obtained from both sexes. Plasma SC-58635 concentrations and PK parameters for each animal are shown in the following table. Tremendous individual variations in PK parameters were noted. Female dogs had higher AUC values and slower clearance rate.

Time (hr)	Plasma SC-58635 Concentrations (μg/ml)			
	Animal Nº			
	32630 (♂)	32631 (♂)	32632 (♀)	32633 (♀)
0.083				
0.167				
0.25				
0.5				
0.75				
1				
1.5				
2				
3				
4				
6				
8				
12				
24				
48				
$\beta_{1/4}$ (hr)				
Cl (ml/min•kg)				
Vd_{area} (l/kg)				
Vdss (l/kg)				
$AUC_{0-\infty}$ (μg•hr/ml)				

ND - below limit of detection o f assay (0.0 25μg/ml)
NSR - no sample received; vial empty
Note: 48 hour data was not used in calculations

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3.1.3.6. Effect Of Growth On The Pharmacokinetics Of SC-58635 After Intravenous Administration To Dogs, Document No.: M3095183; Date: 06-Jun-1997 (Vol. 1.68, p. 265-318)

Study Nº: 6127-256 or MRC-95C-10-950183
Report Nº: M3095183
Study Aim: To determine the effect growth on plasma SC-58635 concentrations and PK following iv administration of SC-58635 to the same dogs at age 14 and 19 months.
Compound: SC-58635 (Lot Nº: 94K031-A1A for Phase 1 study and 95K010-A1A for Phase 2 study) in PEG 400:H_2O (2:1, v/v)
Dose & Route: 5 mg/ml/kg iv single dose at age 14.3-14.8 months and at age 18.7-19.2 months.
Animals: 4♂ and 4♀ beagle dogs previous used for Study MRC-94S-0196, fast clearance 2/sex and slow clearance 2/sex

Study Phase	Study Day	Dose (mg/kg)	Nº of Animals
1	1	5	4♂, 4♀
2	133	5	4♂, 4♀

Study Site:
Compliance with GLP/QAU: N/A

Study Date: Phase 1, 7/19 - 7/21/95 and Phase 2, 11/28 - 12/01/95
Blood Collection: Blood was collected at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr post dose. Analysis of Plasma SC-58635 was Performed by

Results: Mean plasma (±SEM) SC-58635 and PK parameters after iv administration to fast or slow clearance dogs at age of , months old and months old are listed in the following table. Data showed that maturation did not alter metabolism and PK profiles of SC-58635.

Time (hr)	Plasma SC-58635 Concentrations (μg/ml)			
	Fast Clearance		Slow Clearance	
	14.3-14.8 Months Old	18.7 -19.2 Months Old	14.3-14.8 Months Old	18.7 -19.2 Months Old
0.083	3.17 ± 0.13	2.79 ± 0.17	3.31 ± 0.37	3.44 ± 0.37
0.167	2.75 ± 0.22	2.56 ± 0.28	3.23 ± 0.21	3.05 ± 0.18
0.25	2.5 ± 0.21	2.49 ± 0.25	2.93 ± 0.21	2.77 ± 0.21
0.5	2.11 ± 0.25	2.08 ± 0.24	2.61 ± 0.08	2.82 ± 0.27
0.75	1.65 ± 0.2	1.79 ± 0.3	2.36 ± 0.06	2.56 ± 0.19
1	1.44 ± 0.17	1.43 ± 0.21	2.22 ± 0.06	2.03 ± 0.06
1.5	1.06 ± 0.16	1.11 ± 0.17	1.9 ± 0.12	1.94 ± 0.01
2	0.927 ± 0.141	0.892 ± 0.126	1.78 ± 0.06	1.7 ± 0.04
3	0.504 ± 0.13	0.444 ± 0.109	1.21 ± 0.09	1.24 ± 0.08
4	0.344 ± 0.118	0.292 ± 0.086	1.06 ± 0.07	1.02 ± 0.07
6	0.149 ± 0.062	0.115 ± 0.041	0.739 ± 0.066	0.711 ± 0.036
8	0.0771 ± 0.0397	0.0874 ± 0.051	0.507 ± 0.056	0.586 ± 0.013
12	0.0303 ± 0.0243	0.0176 ± 0.0141	0.31 ± 0.062	0.368 ± 0.059
24	BLD	BLD	0.0969 ± 0.0358	0.131 ± 0.045
48	BLD	BLD	BLD	BLD
PK Parameters				
$\beta_{1/2}$ (hr)	1.77 ± 0.39	2.28 ± 0.9	6.08 ± 1.18	7.22 ± 1.61
Cl (ml/min•kg)	16.7 ± 3.0	17.6 ± 3.0	5.59 ± 0.63	5.08 ± 0.45
V_{area} (l/kg)	2.3 ± 0.17	2.85 ± 0.47	2.8 ± 0.33	3.00 ±0.4
Vdss (l/kg)	1.96 ± 0.09	2.12 ± 0.1	2.3 ± 0.25	2.54 ± 0.25
$AUC_{0-\infty}$ (μg•hr/ml)	5.53 ± 1.07	5.29 ± 1.11	15.4 ± 1.5	16.8 ± 1.7

BDL = Below Detection Limit (0.01μg/ml).

3.1.3.7. The Statistical Analysis Of The SC-58635 IV Pharmacokinetic Data In The Dog, Document No.: M3097234; Date: 25-Sep-1997 (Vol. 1.68, p. 319-344)

Report Nº: M3097234
Study Aim: Using the cluster analysis method to evaluate plasma SC-58635 concentration data from 38 dogs in three separate studies (see 3.1.3.5: Report Nº M3095295; 3.1.3.12: Report Nº M3097238; and 3.1.3.13: Report Nº MRC-94S-0196) and to determine whether the two populations could be distinguished by statistical methods.
Compound: SC-58635 in PEG 400:H_2O (2:1, v/v)
Dose & Route: 5 mg/1 ml/kg iv single dose
Animals: 38 beagle dogs
Study Site:
Sample Collection: Blood was collected 5, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hours after dose administration and concentrations of SC-58635 in plasma

assay
Sample Analysis Site:
Study Design: In the present study, the cluster analysis method was used to evaluate the plasma SC-58635 concentration data obtained from three separate iv pharmacokinetic studies 3.1.3.5: Report Nº M3095295; 3.1.3.12: Report Nº M3097238; and 3.1.3.13: Report Nº MRC-94S-0196) to

determine whether this phenomena could be distinguished using statistical methods. The pharmacokinetic parameters were summarized across the three studies by population.

Results: Cluster analysis revealed that there are two populations of dogs: those that eliminate SC-58635 from plasma at a fast and those that eliminate SC-58635 at a slow rate. There is no sex-related difference in the distribution of these two populations. A summary of mean (±SEM) PK parameters is presented in the following table.

PK Parameters	Fast			Slow		
	♂ (N=11)	♀ (N=8)	♂ + ♀	♂ (N=8)	♀ (N=11)	♂ + ♀
$T_{½}$ (hr)	1.77 ± 0.25	1.66 ± 0.16	1.72 ± 0.25	4.69 ± 0.44	5.54 ± 0.36	5.18 ± 0.29
Clp (ml/hr•kg)	19.2 ± 2.2	16.9 ± 1.2	18.2 ± 1.5	7.43 ± 0.44	6.95 ± 0.45	7.15 ± 0.32
Vd (l/kg)	2.63 ± 0.43	2.32 ± 0.15	2.5 ± 0.24	2.95 ± 0.21	3.27 ± 0.21	3.14 ± 0.15
Vdss (l/kg)	2.18 ± 0.20	1.98 ± 0.05	2.10 ± 0.11	2.26 ± 0.09	2.45 ± 0.09	2.37 ± 0.07
$AUC_{0-\infty}$ (μg•hr/ml)	4.95 ± 0.47	5.20 ± 0.47	5.05 ± 0.36	11.5 ± 0.7	12.5 ± 0.7	12.1 ± 0.5

3.1.3.8. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095231; Date: 05-Dec-1997 (Vol. 1.68, p. 345-410)

Report Nº M3095231
Study Aim: To determine the plasma SC-58635 concentrations following IV administration of SC-58635 and oral administration of SC-58635 in a solution, in two capsule formulations and in two tablet formulations.
Compound: SC-58635 (lot Nº GDS4695-042)
IV Solution: 5 mg/ml in PEG 400:H_2O (2:1, v/v)
Oral Solution: 2 mg/ml in PEG 400:H_2O (2:1, v/v)
Capsule A:

Capsule B:

Tablet C:
Tablet D:

Dosage & Route: Single dose of 5 mg/kg iv or po
Animals: 4♂ and 4♀ dogs, kg, months old
Study Location:

Compliance with QAU: Not Indicated.
Study Design: This was a nonrandomized crossover study and the sequences of dosing were shown in the following table. There was a 7-day (Phases 1, 2, 3, and 4) or a 14-day (Phases 5 and 6) washout between two dosage forms of administrations. Blood samples were collected over 24 (oral dose - at 15 and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 and 24 hr) or 48 hr (iv dose - at 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr) post dose.

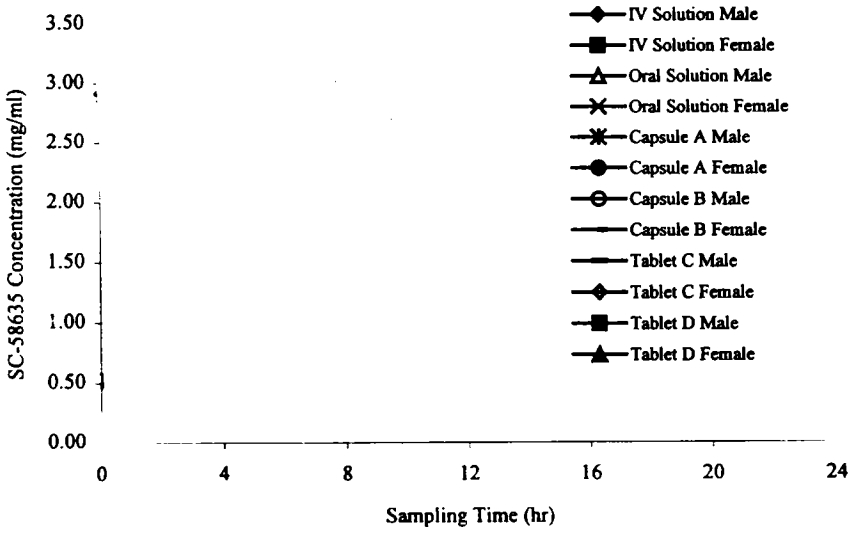
Phase	Dose (mg/kg)	Route	Formulation	Nº of Dogs
1	5	iv	Solution	4/sex
2	5	Oral	Solution	
3	5	Oral	Capsule A	
4	5	Oral	Capsule B	
5	5	Oral	Tablet C	
6	5	Oral	Tablet B	

Results: SC-58635 was absorbed and systemically available following administration in five different dosage forms. Mean plasma SC-58635 levels at various time point following iv and oral

administration in the different dosage forms are presented in the following table. As depicted in the figure, there was no apparent sex-related difference in absorption of test compound.

Sample Time (hr)	Plasma SC-58635 Concentration (µg/ml)											
	IV Solution		Oral Solution		Capsule A		Capsule B		Tablet C		Tablet D	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0.0833	2.915	3.405	-	-	-	-	-	-	-	-	-	-
0.167	2.853	3.175	-	-	-	-	-	-	-	-	-	-
0.25	2.588	2.940	0.560	0.524	0.078	0.141	NM	0.011	NM	0.106	0.057	NM
0.5	2.350	2.383	1.195	0.923	0.098	0.220	0.126	0.022	0.075	0.195	0.151	0.122
0.75	2.065	2.318	-	-	-	-	-	-	-	-	-	-
1	1.890	1.990	1.225	1.121	0.221	0.254	0.349	0.349	0.425	0.245	0.214	0.156
1.5	1.680	1.838	1.198	1.091	0.268	0.290	0.482	0.607	0.316	0.247	0.308	0.126
2	1.392	1.467	1.118	1.051	0.321	0.321	0.495	0.585	0.285	0.231	0.348	0.173
2.5	-	-	1.063	1.005	0.345	0.327	0.514	0.575	0.262	0.155	0.355	0.116
3	1.195	1.257	0.900	0.861	0.336	0.296	0.458	0.527	0.275	0.176	0.323	0.320
4	0.914	1.022	0.686	0.658	0.267	0.234	0.344	0.392	0.216	0.150	0.280	0.427
6	0.456	0.560	0.357	0.421	0.165	0.449	0.344	0.423	0.693	0.509	0.353	0.562
8	0.268	0.386	0.222	0.296	0.247	0.269	0.362	0.373	0.501	0.508	0.286	0.335
12	0.272	0.352	0.124	0.153	0.091	0.114	0.083	0.109	0.073	0.115	0.172	0.065
24	0.145	0.192	0.031	0.048	0.036	0.040	0.031	0.049	0.045	0.041	0.103	0.028

NM = Below lower limit of quantitation, 0.0100 µg/ml.



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3.1.3.9. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095301; Date: 09-Dec-1997 (Vol. 1.69, p. 1-92)

Report Nº M3095301

Study Aim: To determine the plasma SC-58635 concentrations following iv administration of SC-58635 and oral administration of SC-58635 in a solution, in two immediate release capsule formulations, in two immediate release tablet formulations, in one controlled-release capsule formulation and in three controlled-release tablet formulations.

Compound: SC-58635 (lot Nº GDS4695-042)

IV Solution: 5 mg/ml in PEG 400:H_2O (2:1, v/v)

Oral Solution: 2 mg/ml in PEG 400:H_2O (2:1, v/v)

Tablet A:

Tablet C:

Capsule B:

Phase II Capsule: 66.7% SC-58635/2.5% povidone/36% lactose/1.5% magnesium stearate

Capsule D:
Tablet E
Tablet F:
Tablet G:

formulations as stated by the sponsor and detailed ingredients were not disclosed; used for Phases 7, 8, 9 and 10 studies at doses of 5 mg/kg.

Dosage & Route: Single dose of 5 mg/kg iv or po
Animals: 4♂ and 4♀ dogs, kg, months old
Study Location:

Compliance with QAU: Not Indicated.

Study Design: Group of 4/sex Beagle dogs were administered SC-58635 IV in a solution, orally in a solution, in two immediate release tablet formulations, in two immediate release capsule formulations, in one controlled-release capsule formulation and in three controlled-release tablet formulations of SC-58635 in a nonrandomized crossover design as shown in the following table. There was a 7- day washout period between Phases 1, 2 and 3. There was a 28-day washout period between Phases 3 and 4. There was a 40-day washout period between Phases 4 and 5. There was a 14-day washout period between Phases 5, 6 and 7. There was a 28-day washout period between Phase 7 and 8. There was a 7-day washout period between phases 8, 9 and 10. Blood samples were collected over 24 (oral dose - at 15 and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 and 24 hr) or 48 hr (iv dose - at 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr) post dose. Plasma concentrations of SC-58635 were determined using

Phase	Dose (mg/kg)	Route	Formulation	Nº of Animals	
				♂	♀
1	5	IV	Solution	4	4
2	5	Oral	Tablet C		
3	5	Oral	Tablet A		
4	5	Oral	Capsule B		
5	5	Oral	Solution		
6	5	Oral	Phase II Capsule		
7	5	Oral	Capsule D		
8	5	Oral	Tablet E		
9	5	Oral	Tablet F		
10	5	Oral	Tablet G		

Results: Data showed that SC-58635 was absorbed and systemically available following administration. Mean plasma SC-58635 levels at various time point following iv and oral administration in the different dosage forms are presented in the following table. High degree of variability in the plasma concentrations were seen among animals within each dose group.

Time (hr)	IV Solution	Tablet C	Tablet A	Capsule B	Oral Solution	Phase II Capsule	Capsule D	Tablet E	Tablet F	Tablet G
0.0833	3.178	-	-	-	-	-	-	-	-	-
0.167	2.941	-	-	-	-	-	-	-	-	-
0.25	2.825	0.071	1.346	0.389	0.874	0.068	0.154	0.190	0.022	0.021
0.50	2.571	0.240	0.813	0.672	1.323	0.246	0.297	0.412	0.028	0.072
0.75	2.421	-	-	-	-	-	-	-	-	-
1	2.111	0.396	0.507	0.742	0.916	0.258	0.368	0.185	0.056	0.202
1.5	1.833	0.521	0.576	0.690	1.091	0.376	0.389	0.191	0.127	0.347
2	1.665	0.626	0.439	0.666	0.954	0.443	0.399	0.210	0.183	0.505
2.5	-	0.598	0.289	0.628	0.979	0.404	0.371	0.202	0.185	0.583
3	1.476	0.441	0.266	0.530	0.878	0.574	0.364	0.171	0.177	0.538
4	1.322	0.537	0.354	0.460	1.258	0.533	0.320	0.155	0.156	0.509
6	0.887	0.379	0.470	0.328	0.977	0.354	0.229	0.109	0.106	0.366
8	0.699	0.332	0.375	0.251	0.811	0.321	0.209	0.086	0.091	0.316
12	0.496	0.234	0.126	0.185	0.564	0.311	0.187	0.064	0.067	0.284
24	0.324	0.192	0.101	0.134	0.332	0.147	0.141	0.142	0.079	0.368
48	0.141	-	-	-	-	-	-	-	-	-

3.1.3.10. Systemic Availability Of The Cyclooxygenase-2 Inhibitor, SC-58635, In Female Beagle Dogs After Administration Of SC-58635 Intragastrically (IG) Or Directly Through A Chronic Intestinal Access Port (CIAP) Into The Duodenum, Jejunum, Or Colon, Document No.: M3095195; Date: 11-Jun-1997 (Vol. 1.69 p. 93-125)

Report Nº: M3095195
Study Aims: To determine the primary site(s) of absorption of SC-58635 in the dog GI tract.
Compound: SC-58635 (Lot Nº 94L013-A1A) in PEG 400/saline (2:1)
Vehicle: PEG 400/saline (2:1)
Dose and Route: 10 mg/kg intragastrical injection or injected directly through CIAP in to the duodenum, jejunum or colon
Animals: 4 CIAP ♀ dogs, kg
Study Site: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/AUC: N/A
Study Design: Four ♀ surgical prepared and 3 Chronic Intestinal Access Ports (CIAP) directly accessible to the upper duodenum, jejunum and colon were permanently implanted. SC-58635, 10 mg/kg, were injected intragastrically or directly through CIAP in to the duodenum, jejunum or colon. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, and 24 hr post dosing.
Results: Mean (±SM) plasma concentrations (μg/ml) of SC-58635 and pharmacokinetic parameters after administration of 10 mg SC-58635/kg intragastrically (ig) or directly through a CIAP into the duodenum, jejunum or colon of female beagle dogs are listed in the following table.

Time (hr)	IG	Duodenum	Jejunum	Colon
0	0	0	0.0113 ± 0.0113	0.007 ± 0.004
0.25	1.40 ± 0.42	1.17 ± 0.22	0.908 ± 0.246	0.109 ± 0.018
0.5	1.49 ± 0.38	1.23 ±0.25	0.902 ± 0.288	0.140 ± 0.028
0.75	1.39 ± 0.34	1.20 ± 0.21	0.858 ± 0.255	0.188 ± 0.045
1	1.39 ± 0.33	1.13±0.16	0.847 ± 0.252	0.223 ± 0.060
1.5	1.31 ± 0.28	1.12 ± 0.15	0.782 ± 0.165	0.301 ± 0.084
2	1.15 ± 0.24	1.03 t 0.20	0.717 ± 0.125	0.363 ± 0.111
3	0.945 ± 0.182	0.969 ± 0.204	0.595 ± 0.081	0.473 ± 0.164
5	0.633 ± 0.135	0.911 ± 0.350	0.487 ± 0.07	0.675 ± 0.161
8	0.391 ± 0.078	0.391 ± 0.075	0.464 ± 0.084	0.620 ± 0.074
12	0.287 ± 0.057	0.208 ± 0.043	0.333 ±0.076	0.534 ± 0.093
24	0.0901 ± 0.0257	0.0433 ± 0.0228	0.177 ± 0.084	0.098 ± 0.030
C_{max} (μg/ml)	1.62 ± 0.36	1.46 ± 0.20	1.06 ± 0.21	0.789 ± 0.118
T_{max} (hr)	0.688 ± 0.277	1.13 ± 0.63	2.25 ± 1.92	8.50 ± 2.02
AUC_{0-24} (μg•hr/ml)	10.3 ± 2.0	9.69 ± 1.57	9.37 ± 0.97	10.00 ± 0.9

3.1.3.11. The Bioavailability of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095048; Date: 14-May-1996 (Vol. 1.69, p. 126-179)

Study Nº MRC-95S-0048 6127-235
Report Nº M3095048
Study Aim: To determine plasma concentrations of SC-58635 following administration of the compound to dog in several different capsule formulations.
Compound: SC-58635
Solution: in PEG 400 : H_2O (2:1, v/v)
Formulation A:
Formulation B:
Formulation C:

Formulation D:
Dosage & Route: Single dose of 5 mg/kg po
Animals: Healthy 3♂ & 3♀ dogs, months of age, weighing kg, 3/sex/group
Study Location:
Compliance with QAU: Not Indicated.
Study Design: This was a nonrandomized crossover study. There was a 7-day washout between two dosage forms of administrations. Blood samples were collected at 0 and 30 min, and 1, 1.5, 2, 2.5, 3.5, 7, and 24 hr post each dosing. Plasma SC-58635 levels were determined using an HPLC method.

Group	Dose (mg/kg)	Formulation	Route	Nº of Animals	
				♂	♀
1	5	Solution	po (gavage)	3	3
	5	A (Gelatin Capsule)	po		
	5	B (Gelatin Capsule)	po		
2	5	C (Gelatin Capsule)	po	3	3
	5	D (suspension)	po (gavage)		

Results: Plasma SC-58635 levels and mean PK parameter (n=3) of dogs receiving different formulations of SC-58635 are presented in the following table. It appeared that SC-58635 was systemically absorbed following oral administration of SC-58635 in the five different formulations. High degree of variability in the plasma concentrations were seen among animals within each dose group. The bioavailability (BA) for SC-58635 was superior in the solution or suspension form.

Sampling Time (hr)	Plasma SC-58635 Concentration (Mean ± SEM), μg/ml									
	Solution		Formulation A		Formulation B		Formulation C		Formulation D	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0.25	0.975	0.509	0.006	0	0.022	0.115	0	0	0.138	0.081
0.5	1.52	0.824	0.093	0.005	0.094	0.247	0.072	0.064	0.334	0.453
1	1.37	0.820	0.215	0.244	0.271	0.228	0.200	0.443	0.608	0.826
1.5	1.23	0.762	0.353	0.357	0.355	0.189	0.529	0.672	0.762	0.936
2	1.08	0.604	0.421	0.318	0.381	0.138	0.586	0.717	0.729	0.865
2.5	0.853	0.594	0.362	0.243	0.282	0.101	0.537	0.586	0.643	0.800
3	0.780	0.517	0.315	0.189	0.265	0.086	0.437	0.492	0.539	0.741
4	0.628	0.413	0.228	0.145	0.234	0.071	0.332	0.384	0.447	0.576
6	0.436	0.286	0.167	0.107	0.278	0.066	0.213	0.233	0.304	0.354
8	0.303	0.187	0.157	0.083	0.210	0.062	0.160	0.160	0.234	0.234
12	0.163	0.080	0.219	0.094	0.190	0.043	0.105	0.087	0.183	0.142
24	0.004	0.016	0.083	0	0.103	0.040	0.033	0.041	0.058	0.039
C_{max} (μg/ml)	1.52	0.839	0.524	0.36	0.453	0.250	0.639	0.785	0.826	1.01
T_{max} (hr)	0.5	0.667	5.33	1.33	3.33	0.667	1.5	1.5	5.17	1.67
AUC_{0-24} (μg•hr/ml)	7.93	4.7	4.34	1.89	4.56	1.53	3.72	4.06	5.72	6.11
BA (%)	89.4	62.4	49.4	31.2	52.2	24.9	42.9	46.3	87.5	69.5

3.1.3.12. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3097238; Date: 06-Aug-1997 (Vol. 1.69, p. 180-297)

Report Nº: M3097238

Study Aims: To determine the plasma SC-58635 concentrations and PK following iv administration and oral administration in different capsule and tablet formulation.

Compound: iv formulation - SC-58635 (Lot Nº: 96K001-A3A) in PEG400/sterile H_2O (2:1, v/v)
oral tablet formulation - A (GDS-6115-051A), B (GDS6115-051B) and C (GDS6115-051F)
oral capsule formulation - D, E, F, and H (PT-128-96 and PT121-96)

Dose and Route: 5 mg/kg iv with a 29-day washout period;
40, 40 and 60 mg/kg for oral tablet formulation A, B, and C, respectively with a 7-day washout period;
50 mg/kg for capsule formulation D, E, F, and H (crossover with a 7-day washout period)

Animals: beagle dog

Study Site:

Study Design: Five ♂ and five ♀ beagle dogs were administered intravenously (iv) SC-58635 in polyethylene glycol (PEG) 400:sterile water (2: 1, v/v) at a single dose of 5 mg/kg. One male and three female dogs were selected from the original ten animals and were orally administered three different tablet formulations of SC-58635 (formulations A, B, & C) at single doses of 40, 40 and 60 mg/kg and four different capsule formulations of SC-58635 (formulations D, E, F & H) at single doses of 50 mg/kg in a nonrandomized crossover design.

Blood Collection: 5, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hr post iv administration;
15 and 30 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hr post oral dosing.

Results: The plasma $T_{½}$ and clearance of SC-58635 for ♂ and ♀ dogs after iv administration of 5 mg/kg SC-58635 and the $T_{½}$, C_{max}, and $AUC_{0-\infty}$ values of SC-58635 after oral administration of 50 mg/kg SC-58635 in capsule formulation H are shown in the following table. SC-58635 was absorbed and systemically available following oral administration of formulations A, B, C, D, E, F and H.

Dose (mg/kg)	Route	Sex	$T_{½}$ (hr)	Clp (ml/min•kg)	Vd_{ss} (l/kg)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
5	iv	♂	1.56 to 3.83			-	-
		♀	1.52 to 5.63			-	-
50 (Capsule H)	po	♂ & ♀	1.00 to 3.00	-	-		

3.1.3.13. The Pharmacokinetics Of SC-58635 Following Single Intravenous And Oral Multiple Dose Administration to Dogs, Document No.: MRC-94S-0196; Date: 07-Dec-1995 (Vol. 1.69, p.298-409)

Report Nº MRC-94S-0196

Study Nº 6127-229

Study Aim: To determine the PK of SC-58635 following administration of SC-58635 as a neat compound or as a formulated mixture to the dogs with or without meal feeding.

Compound: SC-58635 (Lot Nº 94K014-A2B) in gelatin capsule or PEG:H_2O (2:1, v/v)for Phase I, III and IV studies; formulated SC-58635 in 5 mg capsule (RTC 9673) for Phase II study.

Dosage: Phase I & II - 5 or 15 mg/kg po for 14 days for; Phase III - 5 mg/kg iv for; Phase IV- 25 mg/kg po for 14 days
Animals: 12♂ and 12♀ beagle Dogs
Study Site:
Compliance with QAU: N/A
Experimental Design:

- Phase I (Days 1-14 of the study): Dogs were administered orally SC-58635 as a neat chemical in a gelatin capsule at 5 or 15 mg/kg/day for 14 days.
- Phase II (Days 21-35 of the study): Dogs were administered orally SC-58635 in **formulated capsules** at 5 or 15 mg/kg for 14 days.
- Phase III (Day 51 of the study): SC-58635 was administered to the dogs in Groups 1 and 2 intravenous (IV) at a dose of 5 mg/kg.
- Phase IV (Days 78-92 of the study): Dogs were administered orally SC-58635 as neat compound in gelatin capsules at 25 mg/kg for 14 days with or without food.

Results: There are two distinct populations in both male and female dogs that eliminate SC-58635 from plasma at either a fast or slow rate. The pharmacokinetics following IV administration of SC-58635 were not different between male and female dogs. Fast SC-58635 clearance animals had higher exposure to SC-58635 (as measured by C_{max} and AUC). T_{max} of SC-58635 was prolonged when the compound was coadministered to dogs with food. Mean PK parameters either analyzed by the sex or by the rate of clearance from each phase (except Phase III) study are summarized in the following tables.

Phase I:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase I of the Study

Day	Dose mg/kg/day	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
1	5	3.33 ± 1.74	1.5 ± 0.18	0.287 ± 0.046	0.525 ± 0.168	2.49 ± 0.84	2.9 ± 1.12
	15	2.42 ± 0.42	2.92 ± 0.64	0.853 ± 0.097	1.92 ± 0.47	4.91 ± 0.71	14.2 ± 3.4
14	5	1.67 ± 0.17	1.42 ± 0.08	0.281 ± 0.07	0.357 ± 0.039	2.15 ± 0.62	1.62 ± 0.88
	15	3.17 ± 1.77	3.5 ± 1.17	0.439 ± 0.79	1.2 ± 0.23	3.27 ± 1.11	9.8 ± 2.36

- Mean (±SEM) SC-58635 Pharmacokinetic Parameters (Analyzed by the Rate of Clearance) for Phase I of the Study

Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.50 ± 0.22	0.229 ± 0.046	0.950 ± 0.333
1		S	6	3.33 ± 1.74	0.583 ± 0.146	4.44 ± 0.80
14		F	6	1.50 ± 0.13	0.250 ± 0.055	0.818 ± 0.221
14		S	6	1.58 ± 0.15	0.389 ± 0.044	2.95 ± 0.18
1	15	F	3	2.17 ± 0.67	0.870 ± 0.077	3.80 ± 0.75
1		S	9	2.83 ± 0.45	1.56 ± 0.36	11.5 ± 2.6
14		F	3	1.67 ± 0.33	0.384 ± 0.117	1.38 ± 0.46
14		S	9	3.89 ± 1.54	0.965 ± 0.192	8.25 ± 1.76

Phase II:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study

Day	Dose	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	mg/kg/day	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
1	5	1.33 ± 0.11	1.25 ± 0.11	0.306 ± 0.042	0.297 ± 0.018	2.56 ± 0.57	1.44 ± 0.30
	15	3.25 ± 1.76	3.00 ± 1.06	0.615 ± 0.107	1.03 ± 0.26	4.24 ± 0.88	7.64 ± 2.71
14	5	1.17 ± 0.11	1.67 ± 0.38	0.347 ± 0.057	0.547 ± 0.085	2.73 ± 0.74	2.47 ± 0.65
	15	1.25 ± 0.17	1.83 ± 0.36	0.681 ± 0.134	0.998 ± 0.250	4.22 ± 1.14	8.55 ± 2.92

- Mean (± SEM) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study : Compound Administered as Neat Chemical in Gelatin Capsule

Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.33 ± 0.11	0.279 ± 0.016	0.972 ± 0.132
1		S	6	1.25 ± 0.11	0.324 ± 0.040	3.03 ± 0.32
14		F	6	1.17 ± 0.11	0.453 ± 0.110	1.17 ± 0.31
14		S	6	1.67 ± 0.38	0.441 ± 0.048	4.02 ± 0.27
1	15	F	3	1.67 ± 0.44	0.841 ± 0.210	3.43 ± 1.33
1		S	9	3.61 ± 1.28	0.815 ± 0.188	6.77 ± 1.83
14		F	3	1.33 ± 0.17	0.451 ± 0.127	1.52 ± 0.06
14		S	9	1.61 ± 0.27	0.968 ± 0.166	8.01 ± 1.89

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Phase III: No data were presented.

Phase IV:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase IV of the Study

Day of Dosing	Dose mg/kg	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
COMPOUND ADMINISTERED WITH FOOD							
1	25	9.67 ± 1.09	8.92 ± 1.96	2.41 ± 0.40	1.52 ± 0.41	25.9 ± 6.4	11.7 ± 3.1
14	25	7.83 ± 2.33	8.67 ± 2.11	2.34 ± 0.70	1.29 ± 0.28	27.8 ± 10.8	9.62 ± 2.28
COMPOUND ADMINISTERED WITHOUT FOOD							
1	25	3.67 ± 1.68	6.58 ± 1.93	1.18 ± 0.35	3.16 ± 0.79	7.57 ± 2.74	38.1 ± 11.5
14	25	4.00 ± 1.62	3.67 ± 0.53	1.69 ± 0.74	4.56 ± 1.00	12.3 ± 6.25	52.5 ± 17.5

- Mean (± SEM) (by Clearance) Pharmacokinetic Parameters of SC-58635, 25 mg/kg iv, for the Phase IV Study

Day of Dosing	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
COMPOUND ADMINISTERED WITH FOOD					
1	F	6	9.00 ± 1.61	1.38 ± 0.33	8.42 ± 1.82
1	S	6	9.58 ± 1.56	2.55 ± 0.41	29.10 ± 5.0
14	F	6	8.25 ± 1.86	1.35 ± 0.28	7.78 ± 2.31
14	S	6	8.25 ± 2.54	2.29 ± 0.72	29.60 ± 10.1
COMPOUND ADMINISTERED WITHOUT FOOD					
1	F	3	5.67 ± 3.17	1.18 ± 0.25	7.51 ± 3.97
1	S	9	4.94 ± 1.49	2.50 ± 0.65	28.00 ± 9.1
14	F	3	3.17 ± 0.33	1.84 ± 0.53	11.90 ± 6.4
14	S	9	4.06 ± 1.09	3.55 ± 0.94	39.30 ± 13.6

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3.1.3.14. The Pharmacokinetics Of SC-58635 Following Multiple Dose (Q.D. And B.I.D.) Administration To Dogs, Document No.: MRC-95S-0050; Date: 02-Feb-1996 (Vol. 1.69, p. 410-457)

Report Nº MRC95S-005 6127-237)